FORMULATION AND EVALUATION OF ORAL DISPERSIBLE TABLET OF TRAMADOL HYDROCHLORIDE

Dissertation Submitted to

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MASTER OF PHARMACY
In
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By

Reg. No: 26101005

Under the Guidance of

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THE CERTIFICATE

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DECLARATION

I do hereby declare that the thesis entitled **"FORMULATION AND EVALUATION OF ORAL DISPERSIBLE TABLET OF TRAMADOL HYDROCHLORIDE"** by **Reg. No: 26101005** submitted in partial fulfillment for degree of **Master of Pharmacy in Pharmaceutics** was carried out at C.L.Baid Metha college of Pharmacy, Chennai-97 under the guidance and supervision of **DR. R.KUMARAVELRAJAN M. Pharm., Ph.D.,** and industrial guide **Mr.Ramesh Jagadeeshan, M.Pharm.,** during the academic year 2011-2012. The work embodied in this thesis is original, and is not submitted in part or full for any other degree of this or any other University.

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ABBREVIATIONS

FTIR	Fourier transformer infrared spectroscopy
HCL	Hydrochloric Acid
HPLC	High performance liquid chromatography
HPMC	Hydroxy propyl methyl cellulose
HPβCD	Hydroxypropyl β cyclodextrin
IR	Infrared spectroscopy
MCC	Micro crystalline cellulose
MDT	Mouth Dissolving Tablets
ODT	Oral Dispersible Tablets
PVP	Polyvinylpyrrolidine
SSG	Sodium starch glycolate
UV	Ultraviolet
XG	Xanthan gum

NOMENCLATURE

%	Percentage
µg/ml	Microgram/millilitre
Conc	Concentration
gm/cc	Gram/cubic centimetre
Hr	Hour
Kg/cm^2	Kilogram/square centimetre
Min	Minute
Mm	Millimetre
Ng	Nanogram
ng/ml	Nanogram/millilitre
ng-hr/ml	Nanogram-hour/millilitre
Nm	Nanometer
SD	Standard Deviation
Sec	Seconds

CONTENTS

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(Reg.No: 26101005)

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desire therapeutics concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment[1].

Drugs are frequently taken by oral administration. Although a few drugs taken orally are intended to be dissolved within the mouth, majority of drugs taken orally are swallowed. Compared with alternate routes, the oral route of drug administration is the most popular and has been successfully used for conventional delivery of drug. It is considered as most natural, convenient means of administering drugs[2].

One important drawback of these dosage forms was many patients have difficulty in swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy[3]. It has been reported that dysphagia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea[4].

This problem can be resolved by the creation of rapidly dispersing or dissolving oral forms, which do not require water to aid swallowing. The dosage forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way[3].

1.1 *Oral Dispersible Tablet*

This is an innovative tablet technology where the dosage form containing active pharmaceutical ingredients disintegrates rapidly, usually in a matter of seconds, without the need for water, providing optimal convenience to the patient. Innovators and inventor companies have given these tablets various names such as Orally disintegrating tablets (ODT), Mouth dissolving (MD), Fast melting, Fast

dissolving, Fast dispersing, Rapid dissolve,Rapid melt, Quick disintegrating, Rapimelts, Melt-in-mouth tablets, Porous tablets or Orodisperse [5, 6].

British Pharmacopoeia defines oral dispersible tablets as uncoated tablets intended to be placed in the mouth were they disperse rapidly before being swallowed[7].

1.2 *Criteria for developing Oral Dispersible Tablets* [5, 8, 9]

Tablets should

- Not require water to swallow, and should disintegrate or dissolve in mouth in matter of seconds.
- Have an acceptable taste masking.
- Leave minimal or no residue in mouth after administration.
- Have a pleasant mouth feel.
- Be less sensitive to environmental conditions such as temperature and humidity.

1.3 *Salient features of Oral Dispersible Tablets* [5, 9]

- Do not require water to swallow, which is convenient during travelling and who do not have immediate access to water.
- Ease of administration to the patients who are unable to swallow, such as bedridden patients, stroke victims and patients who refuse to swallow such as geriatric, pediatric & psychiatric patients.
- Some drugs may be absorbed from the mouth, pharynx and esophagus as the saliva passes down into stomach in those cases bioavailability of the drug is increased.
- The risk of suffocation during oral administration of conventional tablet due to physical obstruction is avoided.

- Good mouth feel property helps to change the perception of medication as bitter pill.

1.4 *Benefits of Oral Dispersible Tablets* [5, 10]

- Administered without water anywhere and anytime.
- Suitability for geriatric, pediatric, and bedridden or developmentally disabled patients, patients with persistent nausea.
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

1.5 *Limitations of Oral Dispersible Tablets* [5, 8, 9, 10]

- The tablets usually have low mechanical strength, so they are friable or brittle and difficult to handle. So they require specialized peel-off blister packing and careful handling.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.
- Drugs with relatively large doses are difficult to formulate into oral dispersible tablets.

- Patients with Sjogren's syndrome or dryness of mouth due to decreased saliva production may not be good candidates for this formulation.
- Patients who concurrently take anti cholinergic medication are not suitable for oral dispersible tablets.

1.6 *Challenges of Oral Dispersible Tablets* [9, 10, 11]

1.6.1 Fast Disintegration

ODTs should disintegrate in the mouth without the aid of water or with a very small amount of water. The "fast disintegration" usually means disintegration of tablets in less than 1 minute, but it is preferred to have disintegration as soon as possible. The disintegration fluid is provided by the saliva of the patient.

1.6.2 Palatability

Oral dispersible tablets dissolve or disintegrate near the taste buds. A pleasant taste inside the mouth becomes critical for patient acceptance. Unless the drug is tasteless or does not have an undesirable taste, taste-masking techniques should be used. An ideal taste-masking technique should provide good mouth feel and should be compatible with ODT formulations. The amount of taste masking material should be as low as possible to reduce the tablet size.

1.6.3 Tablet Strength and Porosity

In order to disintegrate the oral dispersible tablet in the oral cavity, the tablet structure should have a highly porous network and should use low compression force, which makes the tablets friable or brittle, which is difficult to handle. Because the strength of a tablet is related to compression pressure, it is important to find the porosity that allows fast water absorption while maintaining high mechanical strength.

1.6.4 Hygroscopicity

Generally oral dispersible tablets are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. This problem can be especially challenging because many highly water soluble excipients are used in the formulation to enhance fast dissolving properties as well as to create good mouth feel. Those highly water soluble excipients are susceptible to moisture. Hence they need protection from various environmental conditions.

1.6.5 Size of Tablet

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8mm while the easiest size to handle was one larger than 8mm. Therefore, the tablet size that is easy to take and easy to handle is difficult to achieve.

1.6.6 Amount of Drug

ODTs are limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400mg for insoluble drugs and less than 60mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films.

1.7 *Techniques Used For the Formulation of Oral Dispersible Tablets*

Many techniques have been reported

1.7.1 Freeze-Drying or Lyophilization [12, 13, 14]:

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer and the mixture is dosed by weight and poured in the wells of the bluster packs. The trays holding the blister packs are passed through liquid nitrogen

freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminum foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped. The freeze-drying technique has improved absorption and increase in bioavailability.

Disadvantages:

* Expensive and time consuming
* Fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

1.7.2 Tablet Molding [15, 16]

Molding process is of two types

- **Solvent method:** Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is than removed by air-drying. The tablets manufactured in this manner are less compact than the compressed tablets and posses a porous structure that hastens dissolution.
- **Heat method:** Heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°C under vacuum.

The mechanical strength of molded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology. The taste masked drug particles were prepared by spray congealing, a molten mixture of

hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol, and an active ingredient, into a lactose based tablet triturate form. Compared to the lyophillization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture.

1.7.3 Spray Drying [17, 18]

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose or crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate & croscarmellose sodium and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

1.7.4 Sublimation [19, 20, 21]

To generate a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride may be compressed along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane, benzene can be used as pore forming agents.

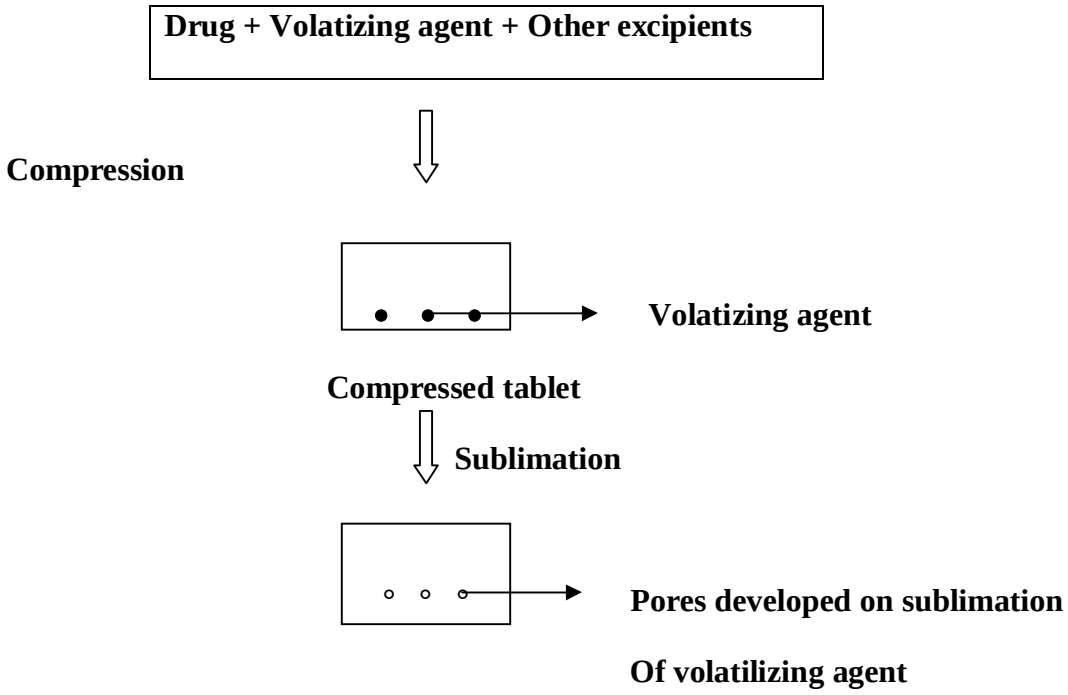

Fig 1: Steps involved in Sublimation

1.7.5 Direct Compression [22, 23]

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied for the preparation of ODT because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

1.7.5.1 Superdisintegrants

In many orally disintegrating tablet technologies based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

1.7.5.2 Sugar Based Excipients

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouthfeel. Mizumito et al have classified sugar-based excipients into two types on the basis of molding and dissolution rate.

Type 1 saccharides (lactose and mannitol) exhibit low mouldability but high dissolution rate.

Type 2 saccharides (maltose and maltilol) exhibit high mouldability and low dissolution rate.

1.7.6 Cotton Candy Process[24]

The cotton candy process is also known as the “candy floss” process and forms on the basis of the technologies such as Flash Dose30 (Fuisz Technology). An ODT is formed using a candyfloss or shear form matrix; the matrix is formed from saccharides or polysaccharides processed into amorphous floss by a simultaneous action of flash melting and centrifugal force. The matrix is then cured or partially recrystallised to provide a compound with good flow properties and compressibility. The candyfloss can then be milled and blended with active ingredients and other excipients and subsequently compressed into ODT. However, the high processing temperature limits the use of this technology to thermostable compounds only.

1.7.7 Mass-Extrusion [25, 26]

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the

product into even segments using heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

1.8 *Patented Technologies for Mouth Dissolving Tablets* [27-31]

* Zydis Technology.
* Durasolve Technology.
* Orasolve Technology.
* Flash Dose Technology.
* Wow Tab Technology.
* Flash Tab Technology.
* Oraquick Technology.
* Quick –Dis Technology.
* Nanocrystal Technology.

1.8.1 Zydis Technology

Zydis, the best known of the mouth-dissolving/disintegrating tablet preparations, was the first marketed new technology tablet. A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile, and must be dispensed in a special blister pack. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds. A major claim of the Zydis product is increased bioavailability compared to traditional tablets. Because of its dispersion and dissolution in saliva while still in the oral cavity, there can be a substantial amount of pre-gastric absorption from this formulation. Any pre-gastric absorption avoids first-pass metabolism and can be an advantage in drugs that undergo a great deal of hepatic metabolism. There are some disadvantages to the Zydis technology. As mentioned earlier, the Zydis formulation is very lightweight and fragile, and therefore should not be stored in backpacks or the bottom of purses. Finally, the Zydis formulation has poor stability at higher

temperatures and humidities. It readily absorbs water, and is very sensitive to degradation at humidities greater than 65%. Example: loratidine

1.8.2 Orasolve Technology

OraSolve was Cima's first mouth-dissolving/disintegrating dosage form. The OraSolve technology, unlike Zydis, disperses in the saliva with the aid of almost imperceptible effervescence. The OraSolve technology is best described as a mouth disintegrating tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The major disadvantage of the OraSolve formulations is its mechanical strength. The OraSolve tablet has the appearance of a traditional compressed tablet. However, the OraSolve tablets are only lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets. An advantage that goes along with the low degree of compaction of OraSolve is that the particle coating used for taste masking is not compromised by fracture during processing. These formulations can accommodate single or multiple active ingredients and tablets containing more that 1.0 g of drug have been developed. Their disintegration time is less than 30 seconds. The OraSolve formulations are not very hygroscopic. Example: zolmitriptan

1.8.3 Durasolve Technology

DuraSolve is Cima's second-generation mouth-dissolving/disintegrating tablet formulation. Produced in a fashion similar to OraSolve, DuraSolve has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. DuraSolve tablets are prepared by using conventional tabletting equipment and have good rigidity (friability less than that 2%). The DuraSolve product is thus produced in a mouther and more cost-effective manner. DuraSolve is so durable that it can be packaged in traditional blister packaging, pouches or vials. One disadvantage of DuraSolve is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction. Example: risperidone

1.8.4 Flash Dose Technology

The Flash Dose technology utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. This procedure has been patented by Fuisz and is known as Shearform. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue. Flash dose tablets consist of self–binding shearform matrix termed as “floss”. Shearform matrices are prepared by flash heat processing and are of two types. Example: ibuprofen

1.8.5 Wowtab Technology

The Wowtab mouth-dissolving/disintegrating tablet formulation has been on the Japanese market for a number of years. The WOW in Wowtab signifies the tablet is to be given “Without Water”. The Wowtab technology utilizes sugar and sugar-like (e.g., mannitol) excipients. This process uses a combination of low mouldability saccharides (rapid dissolution) and high mouldability saccharide (good binding property).The two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and mouth dissolution rate. Due to its significant hardness, the Wowtab formulation is a bit more stable to the environment than the Zydis or OraSolve. It is suitable for both conventional bottle and blister packaging. The Wowtab product dissolves quickly in 15 seconds or less. Example: famotidine

1.8.6 Flashtab Technology

Prographarm laboratories have patented the Flashtab technology. This technology involves the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, extrusion-spheronization, simple pan coating methods and microencapsulation. The microcrystals of microgranules of the active ingredient are added to the granulated

mixture of excipients prepared by wet or dry granulation, and compressed into tablets. All the processing utilized the conventional tabletting technology, and the tablets produced are reported to have good mechanical strength and disintegration time less than one minute. Example: ibuprofen

1.8.7 Oraquick Technology

The Oraquick mouth-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. The taste masking process does not utilize solvents of any kind, and therefore leads to mouther and more efficient production. Also, lower heat of production than alternative mouth-dissolving/disintegrating technologies makes Oraquick appropriate for heat-sensitive drugs. KV Pharmaceutical claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking. Oraquick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the Oraquick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives. Example: hyoscyamine sulfate

1.8.8 Quick –Dis Technology

Lavipharm has invented an ideal intra-oral mouth dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intra-oral drug delivery system, trademarked Quick-Di, is Lavipharm's proprietary patented technology and is a thin, flexible, and quick-dissolving film. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. The typical disintegration time is only 5 to 10 seconds for the Quick-Di film with a thickness of 2 mm. The dissolving time is around 30 seconds for Quick Di film with a thickness of 2 mm.

1.8.9 Nanocrystal Technology

For mouth dissolving tablets, Elan's proprietary NanoCrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using NanoCrystal technology. NanoCrystal particles are small particles of drug substance, typically less than 1000 nm in diameter, which are produced by milling the drug substance using a proprietary wet milling technique. NanoCrystal colloidal dispersions of drug substance are combined with water-soluble ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds. Example: rapamycin

1.9 *Mechanism of Superdisintegrants* [32, 33, 34]

The tablet breaks to primary particles by one or more of the mechanisms listed below

1.9.1 Wetting

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

1.9.2 Swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

1.9.3 Porosity and capillary action (Wicking):

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

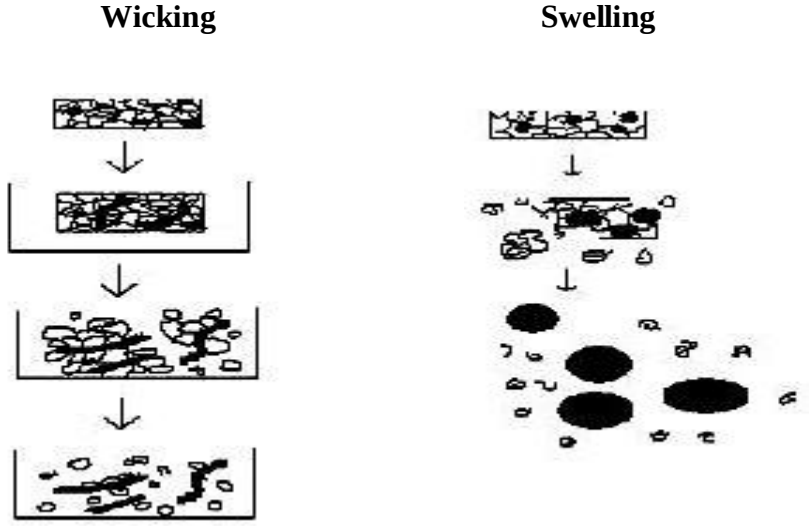

Fig. 2: Disintegration of Tablet by Wicking and Swelling

1.9.4 Particle Repulsive Theory

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrates. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non-swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the

mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

1.9.5 Deformation

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

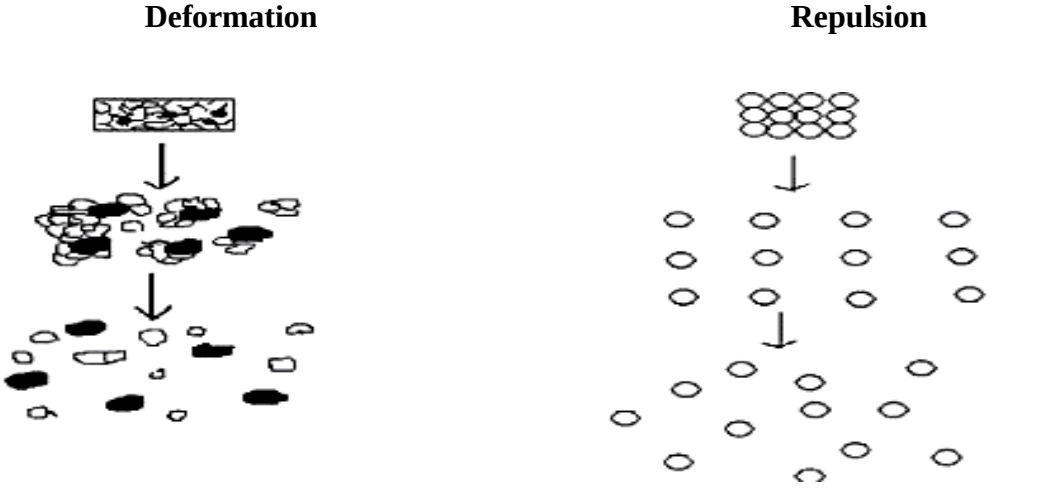

Fig 3: Disintegration of Tablet by Deformation and Repulsion

1.9.6 Release of Gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required

during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

Table 1 List of Superdisintegrants[35]

Superdisintegrants	Example	Mechanism of action	Special comment
Crosscarmellose® **Ac-Di-Sol®** **Nymce ZSX®** **Primellose®** **Solutab®** **Vivasol®** **L-HPC**	Crosslinked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation -Starch free
Crosspovidone **Crosspovidon M®** **Kollidon®** **Polyplasdone®**	Crosslinked PVP	-Swells very little and returns to original size after compression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate **Explotab®** **Primogel®**	Crosslinked starch	-Swells 7-12 folds in < 30 seconds	-Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF **Satialgine®**	Crosslinked alginic acid	-Rapid swelling in aqueous medium or wicking action	-Promote disintegration in both dry or wet granulation
Soy polysaccharides **Emcosoy®**	Natural super disintegrant		-Does not contain any starch or sugar. Used in nutritional products.
Calcium silicate		-Wicking action	-Highly porous, -Light weight -Optimum concentration is between 20-40%

Table 2 Commercially Available Mouth Dissolving Tablets[36]

Technologies	Trade Name	Active Ingredient	Manufacturer
Freeze Drying	Feldene Fast Melt	Piroxicam	Pfizer, USA
	Claritin Redi Tab	Loratidine	Schering plough, USA
	Maxalt MLT	Rizatriptan	Merck, USA
	Zyprexia	Olanzepine	Eli Lilly, USA
	Pepcid RPD	Famotidine	Merck, USA
	Zofran ODT	Ondansetron	Glaxo, UK
	Zooming ZMT	Zolmitriptan	AstraZeneca, USA
	Zelapar TM	Selegilline	Amarin,UK
Disintegrant Addition	Tempra Quicklets	Acetaminophen	Bristol Myers, USA
	Febrectol	Paracetamol	Prographarma, France
	Nimulid MDT	Nimesulide	Panacea Biotech, India
	Torrox MT	Rofecoxib	Torrent pharma, India
	Olanex Instab	Olanzapine	Ranbaxy, India
	Romilast	Montelukast	Ranbaxy, India
Sugar Based Excipient	Benadryl Fastmelt	Diphenhydramine & Pseudoephedrine	WarnerLambert, USA

Literature Review

- Asija Rajesh *et al., (*2012)[37] investigation was to mask the bitter taste of tramadol hydrochloride and develop the orodispersible tablets and study the effect of various factors on percent drug complexation. Ion exchange resins like Kyron-114, Indion-234 and Tulsion-339 were used in different ratios to mask the taste by forming the complex. Superdisintegrants like Kyron-314 and crascarmellose sodium were used in different concentrations and tablets were formulated by direct compression.

- Mansing G. Patil *et al.,* (2011)[38] in their article reviewed taste masking, formulation and evaluation of Tramadol hydrochloride. In the present study an attempt has been made to prepare bitter less orally disintegrating tablet of Tramadol hydrochloride using Eudragit E100 as a taste masking agent. Superdisintegrants like crospovidone, croscarmellose sodium and sodium starch glycolate were used, the prepared blend was evaluated for pre-compressional parameters. Tablets were compressed by Mass extrusion technique and evaluated. Thus the study concludes, successful taste masking and tablets contain crospovidone showed fastest disintegration.

- Ganure Ashok L *et al., (*2011)[39] developed mouth dissolving tablets of tramadol hydrochloride. The bitter taste of drug is prevented by coating granules with isopropanol for specific duration after wet granulation, the granules were then formulated with Aspartame, MCC, Sodium croscarmellose and Sodium starch glycolate and compressed by direct compression technique. Different types of evaluation parameters for the tablets were used. Evaluation of the tablets showed that all the tablets were found to be within official limits.

- Neeharika V *et al.*,(2011)[40] designed to study the difference in disintegration time, wetting efficiency of poorly soluble levofloxacin and freely soluble tramadol hydrochloride using natural and synthetic superdisintegrant. The effect of natural superdisintegrants like isolated mucilage of *Plant ago ovate, Hibiscus rosa-sinensis* and synthetic superdisintegrants like croscarmellose sodium (Ac-Di-Sol) were compared in different concentrations. The blend were evaluated for pre-compression parameters and formulated by direct compression technique. The tablets were evaluated and the physicochemical parameters of dried powdered mucilage were studied. The results showed that natural super disintegrants found to have better disintegration property than the synthetic super disintegrant. The comparative study of poorly soluble levofloxacin and freely soluble tramadol hydrochloride did not show any difference in disintegration time or wetting efficiency with natural or synthetic disintegrants.

- Mahaveer Pr. Khinchi *et al.,* (2011)[41] developed the orally dispersible tablets of Famotidine. Superdisintegrants like Ac-Di-Sol, Crospovidone, Sodium starch glycolate and diluents like dibasic calcium phosphate were used in the formulation of tablets. The tablets were prepared by direct compression and were evaluated. In this study maximum drug release and minimum disintegration time were observed with crospovidone.

- Parikh Bhavik AnjanKumar *et al.,* (2011)[42] designed and evaluated taste mask oral disintegration tablet of lornoxicam. Taste making is done by complexation with β-cyclodextrin by Kneading method. Crospovidone was used as superdisintegrant and tablets were formulated by sublimation technique and effervescent method. The prepared tablets were evaluated. The results showed that the tablets prepared by sublimation technique have more % of drug release than that by effervescent method.

- Ganga Srinivasan *et al.,* (2011)[43] worked in formulation development and evaluation of tramadol hydrochloride orally disintegrating tablets using galen IQ as a diluents. Superdisintegrants like Crospovidone, Croscarmellose sodium, Sodium starch glycolate and Starch 1500. Tablets were prepared by direct compression technique and evaluated. This study suggest that galen IQ could be successfully used as a diluent in the formulation of tramadol hydrochloride orally disintegrating tablet.

- Nitesh J Patel *et al.,* (2011)[44] research was to compare the effect of subliming agents on the oral dispersible property of cinnarizine tablets. Compressed tablets prepared by using soluble material like mannitol which has low porosity. Subliming agents like camphor, menthol, ammonium bicarbonate or thymol were used in the development of oral dispersible tablets by sublimation technique to increase the porosity of the tablets. A high porosity was achieved.

- Sagar Shanti *et al.,* (2011)[45] sustained release implant of tramadol were prepared by extrusion method using specially designed extruder with biodegradable naturally occurring polymer chitosan. By varying the concentration of polymer and crosslinking time, these implants could be used for pain management such as carcinomas, post operative surgery, osteoarthritis, by suitable modification

- Paul *et al.,* (2011)[46] studied the effects of disintegrants in different concentration on the release profile of zidovudine ODTs. Differtent superdisintegrants like crospovidone (PPXL), croscarmellose sodium (Ac-Di-Sol), sodium starch glycolate were used in formulating the tablets by direct compression method. Developed ODTs were studied for their physicochemical properties. Ac-Di-Sol 6% possessed least disintegration time and offered better dissolution profile

- Prakash Goudanavar *et al.,* (2011)[47] develop the orodispersible tablet of lamotrigine. Bitter taste of the drug is successfully masked by forming inclusion complex with hydroxypropyl β-cyclodextrin employing Kneading method. The complex was compressed into tablets along with superdisintegrants such as Kyron T-314, sodium starch glycolate, Indion-414, croscarmellose sodium and crospovidone in different concentration. HPβCD is also useful to enhance the solubility. Orodispersible tablets were characterized by Fourier Transformer Infrared Spectroscopy, Differential Scanning Calorimetry and Powder X-Ray Diffraction Analysis. The prepared tablets were evaluated. Formulation containing higher concentration of Indion-414 decreases disintegration time and optimize the drug release.

- Dayakar Rao Kalakuntla *et al.,* (2011)[48] develop a bitterless oral disintegrating tablet of Lornoxicam. Lornoxiam is a non steroidal anti-inflammatory drug belongs to the class oxicams. Taste masking is done by complexing Lornoxicam with Eudragit E100. Superdisintegrants like sodium starch glycolate and Indion-414. The tablets were evaluated.

- Sunitha S *et al.,* (2011)[49] determine the effect of solvents on microencapsulation tramadol hydrochloride. Solvents like acetone, dimethyldigol, 1,4-dioxan and non-solvents like n-hexane and chloroform. The microspheres were prepared by following coacervation phase separation using various non-aqueous solvents. Microspheres were characterized for the particle size distribution, wall thickness by scanning electron microscopy. The curve fitting data revealed that the release followed first order kinetics.

- Mishra S.K *et al.,* (2011)[50] develop once daily controlled release matrix tablets of Tramadol Hcl. Using different polymers like Eudragit RS-100, Ethylcellulose, Carbopol 934P and Polyvinyl Pyrolidone controlled release matrix tablets of tramadol HCL were

formulated and evaluated. Different release models were applied to *in-vitro* drug release data in order to evaluate the drug release mechanisms and kinetics.

- Shankar Avulapati *et al.,* (2010)[51] this study was to incorporate a combination of superdisintegrants in optimum concentrations which can minimize disintegration time of losartan potassium ODTs. The various superdisintegrants used in the present study were sodium starch glycolate, croscarmellose sodium, crospovidone. Tablets were formulated by direct compression and evaluated for various physicochemical parameters.

- Kumar N *et al.,* (2010)[52] developed fast dissolving tablets of granisetron hydrochloride. A combination of superdisintegrants like sodium starch glycolate-crospovidone, sodium starch glycolate-croscarmellose sodium and sodium starch glycolate-L-hydroxy propyl cellulose were used along with mannitol to enhance mouth feel. Tablets were prepared by direct compression technique and evaluated. Among all formulations, the formulation using 4%w/w sodium starch glycolate and 2%w/w of crospovidone was found to be a promising formulation.

- Suhas M. Kakade *et al.,* (2010)[53] development of orally disintegrating tablets of sertraline to achieve a better dissolution rate. Orally disintegrating tablets which dissolve or disintegrate instantly on the patient tounge or buccal mucosa it is suited for tablets undergoing high first pass metabolism and is used for improving bioavailability. Sertraline is practically slightly soluble in water and extensively absorbed after oral administration, the absolute bioavailability is approximately 44% due to hepatic metabolisim. Superdisintegrants like crospovidone, croscarmellose sodium and sodium starch glycolate were used in formulating tablets by direct compression technique. The tablets prepared were evaluated. Thus the study states that crospovidone showed maximum dissolution rate.

- Sunil H. Makwana *et al.,* (2010)[54] research was to mask the intensely bitter taste of ondansetron Hcl and to formulate a orodispersible of the taste masked drug. Taste masking was done using Indion-204 by solvent evaporation technique in different ratios. Drug-resin complex were optimized by considering parameters such as optimization of resin concentration, swelling time, stirring time, pH and temperature on maximum loading. Resinate was evaluated for taste masking, characterized by X-Ray diffraction and infra red spectrometer. Thus, results conclusively demonstrated successful masking of taste and rapid disintegration of the formulated tablets in the oral cavity.

- Suhas M. Kakade *et al.,* (2010)[55] design the mouth dissolving tablets of losartan potassium with a view to enhance the patient compliance and provide quick onset of action. Due to first pass metabolisim of losartan potassium it has low solubility. Mouth dissolving tablets prepared by direct compression and using superdisintegrants like Polyplasdone XL 10, Croscarmellose sodium and Explotab in different concentration and evaluated for the pre-compression parameters. The prepared batches of tablets were evaluated. Among all formulations Polyplasdone XL 10 was considered to be best formulation.

- B. K. Sridhar *et al.,* (2010)[56] develop and evaluate inclusion complex of isoxsuprine hydrochloride. Taste masking was done by forming inclusion complex with β-cyclodextrin using Kneading method. Tablets were prepared using superdisintegrants like sodium starch glycolate, Ac-Di-Sol, crospovidone by direct compression. The tablets were evaluated. The formulation having Ac-Di-Sol 5% showed complete release of drug.

- Vineet Bhardwaj *et al.,* (2010)[57] objective was to prepare the mouth dissolving tablet of Amlodipine. Superdisintegrants such as Ac-Di-Sol, sodium starch glycolate, Kollidon-CL using different concentrations. Camphor was used as a sublimating agent. Tablets

were prepared by direct compression using mannitol as bulking agent. The compressed tablets are dried for 5 hours to allow sublimation of camphor to increase the porosity and tablets were evaluated. Ac-Di-Sol showed least disintegrating time and fast dissolution.

- S. K. Sheth *et al.,* (2010)[58] develop a taste masked oral disintegrating tablet of poorly soluble lornoxicam. Taste masking is done by complexation with β-cyclodextrin. Various superdisintegrants like sodium starch glycolate, crospovidone, croscarmellose sodium were used in formulating by direct compression method. Prepared tablets were evaluated for various properties and stability studies were conducted as per ICH guidelines. In this study tablets showed enhanced dissolution.

- Jaykar .B *et al.,* (2010)[59] develop orodispersible tablets of terbutaline sulphate which is widely used as a bronchial asthma. Tablets were compressed using ac-di-sol, sodium carboxy methyl cellulose, alginic acid, chitosan and microcrystalline cellulose by direct compression method. Prepared tablets were evaluated.

- N.Kanakadurga devi *et al.,* (2010)[60] develop the formulation for montelukast sodium which overcomes problems such as difficulty in swallowing, inconvenience in administration. Attempt has been made to prepare fast disintegrating tablets of montelukast sodium in the oral cavity. Superdisintegrants like polyplasdone XL 10, Ac-Di-Sol and primojel were used. The pure drug and formulation blend was evaluated for pre-compressional parameters.tablets were prepared by direct compression method and evaluated. Polyplasdone XL 10 was recommended as asuitable disintegrant for the preparation of direct compression melt-in-mouth tablets.

- Metker Vishal *et al.,* (2010)[61] to develop mouth dissolving tablets of lornoxicam. A novel superdisintegrant Kyron T-314(polacrillin

potassium) and menthol as subliming agent were used in the formulation by wet granulation technique. The present study showed rapid absorption, improved bioavailability, effective therapy and patient compliance.

- Vinayak S. Modi *et al.*,(2010)[62] design and evaluate matrix controlled release delivery system of a highly water-soluble analgesic, tramadol hydrochloride using HPMC K 100 M and Xanthan Gum alone and in combination as retarding polymers. Tablets were prepared by direct compression and wet granulation using PVP K 30 as granulating agent. HPMC and XG were used alone. Combinations were designed by using 3^2 – full factorial design. The wet granulation and directly compressed tablets showed good flow property and compressibility. For a water soluble drug single polymer like HPMC K 100 M or Xanthan gum could not retard the release for longer time. But the combination of these polymers significantly retarded the release rate.

- Raval S.B *et al.*,(2009)[63] reported bitter less mouth dissolving tablets of Tramadol hydrochloride using ion-exchange resin Indion-294 as taste masking agent. Ion exchange resinates and tasteless granules were prepared with Indion-294 in the ratio 1:2. The mouth dissolving tablets of both resinates and granules were prepared with different superdisintegrants like Croscarmellose sodium, Crospovidone and Indion-234 in different concentration. The blend was examined for their flow properties and tablets were evaluated for physiochemical properties. The study concluded that tablets prepared by addition of superdisintegrant Indion 234 have less disintegration time, fast and more release than those prepared by crospovidone.

- C.P.Jain *et al.,* (2009)[64] formulated and evaluated fast dissolving tablets of valsartan. Sodium starch glycolate, crospovidone, croscarmellose sodium are the superdisintegrants used. Tablets were prepared by direct compression technique and evaluated for physico-chemical properties. Effect of disintegrant on disintegration

behaviour of tablet in artificial saliva was evaluated. The release of valsartan from fast dissolving tablets was found to follow non-Fickian diffusion kinetics. Crospovidone showed fastest disintegration.

- Neena Bedi *et al.,* (2009)[65] develop the mouth dissolving tablets of oxacarbazepine. In this study mouth dissolving tablets were prepared using two different technologies, direct compression method and solid dispersion technology. Tablets produced by direct compression method contain cospovidone as a super disintegrant and aspartame as a sweetener. Tablets produced by solid dispersion technique contain polyvinylpyrrolidine K-30 and polyethylene glycol 6000 in different ratios to increase its water solubility. The results compared for both the technologies showed that the oxcarbazepine tablets prepared using solid dispersion technology was found to have good technological properties.

- Parmar R.B. *et al.,* (2009)[66] develop a formulation which overcomes problems such as difficulty in swallowing, inconvenience in administration. The present research work was to held to develop fast dissolving tablet of domperidone. Superdisintegrants like sodium starch glycolate used in formulation by direct compression method. All formulations were evaluated.

- Amrit B. Karmarkar *et al.,* (2008)[67] research was to develop *in situ* gelling, bioadhesive nasal inserts of tramadol hydrochloride by lyophilisation of polymer gel solutions. The prepared nasal inserts are a new dosage form having a sponge-like structure. The bioadhesion potential was significantly dependent on the Carbopol 971P: polycarbophil weigh ratio. Diffusion across the nasal mucosa shows a matrix-type profile and the T_{50}% was found to increase as the concentration of polycarbophil increased.

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- Adamo Fini *et al.,* (2008)[68] developed ibuprofen orally disintegrating tablets. To prevent the bitter taste, the drug was associated with Phospholipon-80H, a saturated lecithin, by wet granulation. The granules were then coated using different film forming agents like Kollicoat SR 30, Kollidon-90F, Eudragit RD 100. Coated granules were formulated with superdisintegrants like Kollidon CL or Explotab and a mannitol- based diluents like Pearlitol SD 200. Combined action of hydrophobic lecithin and the coating delay the release of the drug from the tablets. It was thus possible to obtain orally disintegrating tablets and a delayed release of ibuprofen.

- B. Mishra *et al.,* (2006)[69] present study was to formulate and evaluate matrix tablets of tramadol hydrochloride to achieve sustained drug release with reduced frequency of drug administration, side effects and improved patient compliance. Matrix tablets of tramadol HCL were prepared by direct compression technique, using polymers like HPMC, guar gum, xanthan gum alone and in combination in different proportions. The drug release characteristics from matrix tablets were compared with commercial sustained release tablet of tramadol hydrochloride. Matrix tablets having HPMC prolonged the rate and extent of drug release maximally followed by xanthan gum and gaur gum. Increasing percentage of sodium carbonate in core further prolonged the rate and extent of drug release.

Aim and Objective

The aim of the present investigation was to develop the formulation of Tramadol hydrochloride orally dispersible tablet using direct compression technique.

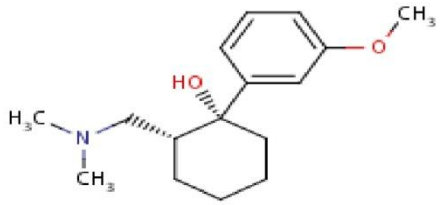
The objective of the study to clarify the effect of different superdisintegrants like Crospovidone (CP), Croscarmellose sodium (CCS), Sodium starch glycolate (SSG) on disintegration and dissolution properties of the drug. The developed formulation tested for all the pharmacoepial and non-pharmacoepial evaluation as orally dispersible tablets.

The optimized formulation also subjected for the stability study as per ICH guidelines and *in vivo* drug release study.

Drug Profile [70, 71, 72]

❖ **Tramadol HCl (USP)**

Structure of Tramadol



IUPAC NAME : 2-(dimethylaminomethyl)-1-(3-methoxyphenyl) cyclohexan-1-ol

Molecular formula : $C_{16}H_{25}NO_2$

Molecular weight : 263.3752 g/mol

Melting point : 180.181 °C

Solubilit : soluble in water

pKa : 9.41

Indications : Indicated in moderate to severe pain in conditions such as

* Arthritis, osteoarthritis and rheumatoid arthritis
* Diabetic neuropathy, trigeminal neuralgia, postoperative neuralgia
* Pain in fractures, disc prolapse, burn, sciatica, dental pains
* Cancer pain

Dose: 50-100 mg every 4 to 6 hours to a maximum dose of 400 mg/day.

Mechanism of Action

Tramadol and its O-desmethyl metabolite (M1) are selective, weak OP3-receptor agonists. Opiate receptors are coupled with G-protein receptors and function as both positive and negative regulators of synaptic transmission via G-proteins that activate effector proteins. As the effector system is adenylate cyclase and cAMP located at the inner surface of the plasma membrane, opioids decrease intracellular cAMP by inhibiting adenylate cyclase. Subsequently, the release of nociceptive neurotransmitters such as substance P, GABA, dopamine, acetylcholine and noradrenaline is inhibited. The analgesic properties of Tramadol can be attributed to norepinephrine and serotonin reuptake blockade in the CNS, which inhibits pain transmission in the spinal cord. The (+) enantiomer has higher affinity for the OP3 receptor and preferentially inhibits serotonin uptake and enhances serotonin release. The (-) enantiomer preferentially inhibits norepinephrine reuptake by stimulating alpha (2)-adrenergic receptors.

Absorption

Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a 100 mg oral dose is approximately 75%.The mean peak plasma concentration of racemic tramadol and M1 occurs at two and three hours, respectively, after administration in healthy adults.

Toxicity	**:**	LD_{50}=350mg/kg (orally in mice)
Protein binding	**:**	20%
Half life	**:**	4to 6hrs

Metabolism

Tramadol undergoes hepatic metabolism via the cytochrome P450 isozyme CYP2D6, being O- and N-demethylated to five different metabolites. Of these,M1 (O-Desmethyltramadol) is the most significant since it has 200 times the μ-affinity

of (+)-tramadol, and furthermore has an elimination half-life of nine hours, compared with six hours for tramadol itself. In the 6% of the population who have slow CYP2D6 activity, there is therefore a slightly reduced analgesic effect. Phase II hepatic metabolism renders the metabolites water-soluble and they are excreted by the kidneys. Thus reduced doses may be used in renal and hepatic impairment.

Adverse Effects

The most commonly reported adverse drug reactions are nausea, vomiting, sweating and constipation. Drowsiness is reported, although it is less of an issue than for other opioids. Respiratory depression, a common side effect of most opioids, is not clinically significant in normal doses. Tramadol can decrease the seizure threshold. When combined with SSRIs, tricyclic antidepressents,or in patients with epilepsy, the seizure threshold is further decreased. Seizures have been reported in humans receiving excessive single oral doses (700 mg) or large intravenous doses (300 mg).

❖ **β-Cyclodextrin** [73]

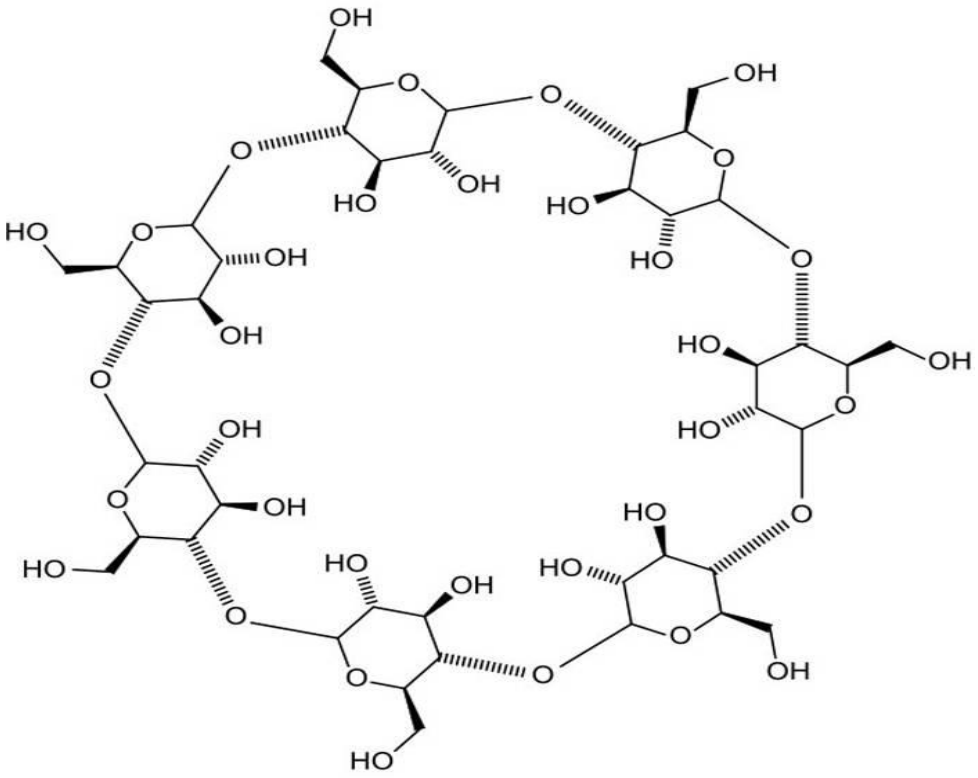
Synonyms : Beta-cyclodextrin, ßCD, BCD, ß-Schardinger dextrin, cyclodextrin B, INS No. 459

Definition : A non-reducing cyclic saccharide consisting of seven alpha-1, 4-linked Dglucopyranosyl units manufactured by the action of cyclodextrin transglycolase on hydrolysed starch followed by purification of the ß-cyclodextrin; purification is by preparation of a ß-cyclodextrin/solvent inclusion compound followed by steam-stripping of the solvent before final purification.

Chemical names : Cycloheptaamylose

Chemical formula : **(**C6H10O5)7

Structural Formula



Formula weight : 1135.00

Description : Virtually odourless, slightly sweet tasting white or almost white crystalline solid

Functional uses : Encapsulation agent for food additives, flavouring and vitamins

Solubility : Sparingly soluble in water; freely soluble in hot water; slightly soluble in ethanol.

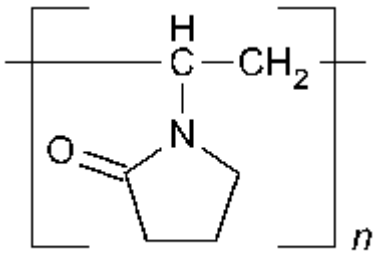
Excipient Profile

❖ **Crospovidone** [74]

Non proprietary Names

BP	:	Crospovidone
PhEur	:	Crospovidonum
USPNF	:	Crospovidone
Synonyms	:	Crosspovidonum ; crospopharm ; croslinked povidone; polyplasdone XL ; polyvinyl polypyrrolidine.
Chemical name	:	1 – ethenyl – 2 - pyrrolidine homopolymer.

Chemical Structure



Description

Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odourless or nearly odourless, hygroscopic powder.

Empirical Formula and Molecular Weight

$(C_6H_9NO)_n$, > 1000000

USP32-NF27 describes crospovidone as a water-insoluble synthetic crosslinked homopolymer of N-vinyl-2-pyrrolidinone.

Applications in Pharmaceutical Formulation

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2-5% concentration in tablets prepared by direct compression or wet and dry-granulation methods. It is rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs.

Typical Properties

P_H	:	5.0 – 8.0
Density	:	1.22 g/cm^3
Moisture Content	**:**	Maximum moisture sorption is approximately 60%.
Solubility	**:**	Practically insoluble in water and most common organic solvents.

Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adduct with some materials like sulfathiazole, sodium salicylate, salicylic acid, Phenobarbital and tannin.

❖ **Croscarmellose sodium**[75]

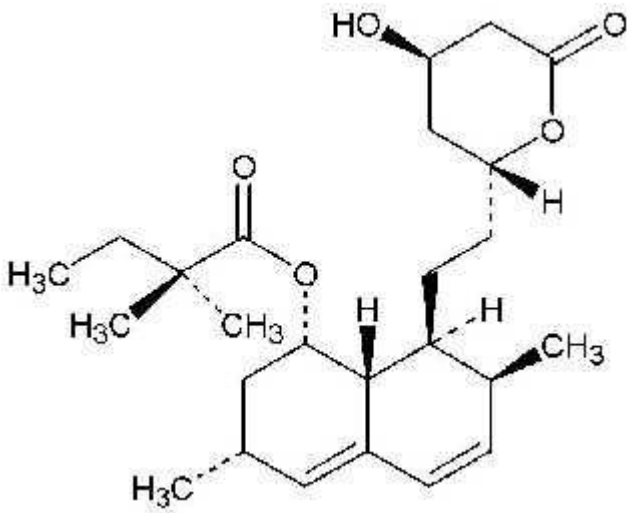
Non Proprietary Name

USPNF: Croscarmellose sodium.

Synonyms

Ac-Di-sol; cross-linked corboxy methylcellulose sodium; Primellose.

Structural Formula



Functional category	**:**	Tablet and capsule disintegrant.
Chemical name	**:**	Cellulose, carboxymethyl ether, sodium salt, cross-linked.
Description	**:**	Croscarmellose sodium occurs as an odourless, white-coloured powder.
Molecular weight	**:**	90000-700000.
PH	**:**	5.0-7.0.

Solubility : Insoluble in water. Although croscarmelose sodium rapidly swells to 4-8 times of its original volume on contact with water.

Stability and Storage Condition

Croscarmellose sodium is stable though it is hygroscopic material. A model tablet formulation prepared by direct compression, with Croscarmellose sodium as disintegrant, showed no significant difference in drug dissolution after storage at 30^0C for 14 months.

Incompatibilities

The efficacy of disintegrants, such as Croscarmellose sodium, may be slightly reduced in tablet formulations prepared by wet granulation or direct compression process which contain which contain hygroscopic material such as sorbitol.

Safety

Croscarmellose is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant material. However, oral consumption of large amount of Croscarmellose sodium may have a laxative effect although the quantities used in solid dosage formulations are unlikely to cause such problems.

Applications : Disintegrant in capsule – 10-25%

Disintegrant in tablets – 0.5-5%

❖ **Sodium Starch Glycolate** [76]

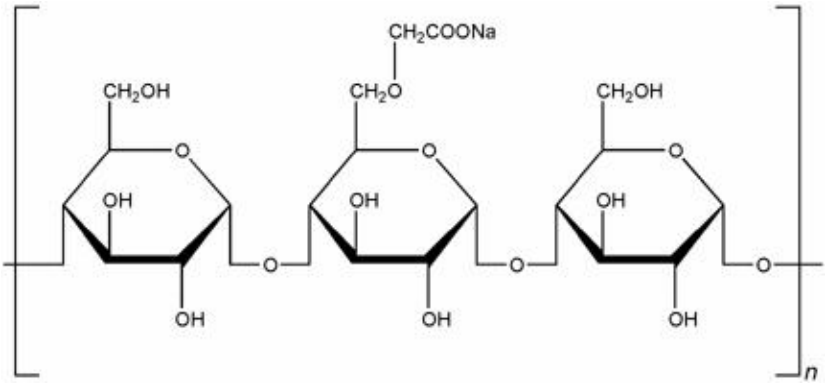
Non proprietary Name

BP : Sodium starch glycolate

USPNF : Sodium starch glycolate.

Synonyms : Explotab, Primogel.

Structural Formula



Functional category : Tablet and capsule disintegrant.

Chemical names : Sodium carboxymethyl starch.

Description

Sodium starch glycolate is a white to off-white, odourless, tasteless, free flowing powder. It consists of oval or spherical granules, 30-100 μm in diameter with some less spherical granules ranging from 10-35 μm in diameter.

Solubility : Practically insoluble in water; sparingly soluble in ethanol (95%). In water it swells upto 300 times its volume.

Stability and Storage Conditions: It is a stable material. It should be stored in a well closed container to protect from wide variations in humidity and temperature that may cause cracking.

Incompatibilities : Incompatible with ascorbic acid.

Safety : It is generally regarded as non-toxic and non-irritant material. However, oral ingestion of large quantities may be harmful.

Applications : As a disintegrant in tablet (wet granulation and direct compression) and capsule formulation in 2-8% concentration.

❖ **Micro Crystalline Cellulose**[77]

Non Proprietary Names

BP : Microcrystalline Cellulose

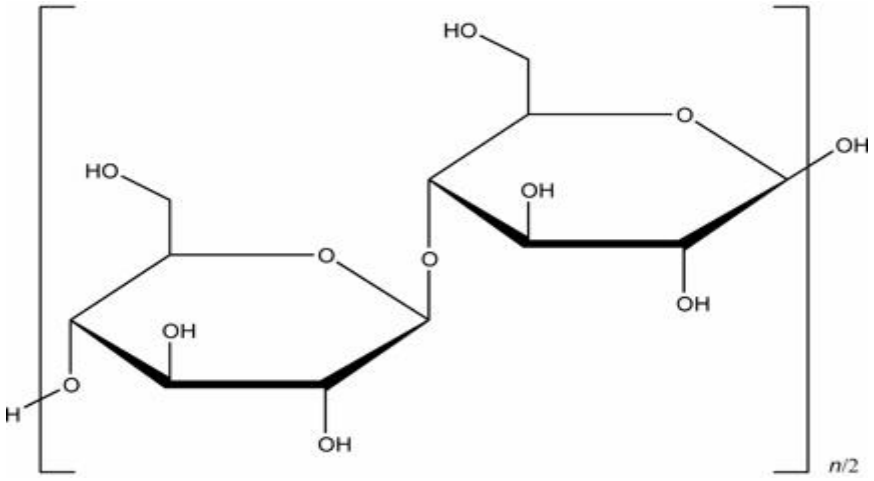
JP : Microcrystalline Cellulose

PhEur : Cellulose, Microcrystalline

USP-NF : Microcrystalline Cellulose

Synonyms : Avicel PH; Celex; Cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; ethispheres .

Structural Formula



Description : Microcrystalline cellulose is a purified partially depolymerised cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Chemical Name : cellulose

Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ 36000

where n=220

Functional Category : Adsorbent; suspending agent; tablet and capsule diluents; tablet disintegrant.

Stability and Storage Conditions

Microcrystalline cellulose is a stable through hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities : Microcrystalline cellulose is a incompatible with strong oxidizing agents.

Applications

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluents in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluents, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

❖ **Colloidal Silicone Dioxide (Aerosil)** [78]

Nonproprietary Names

BP	:	Colloidal anhydrous silica
PhEur	:	Silica colloidalis anhydrica
USPNF	:	Colloidal silicon dioxide

Synonyms	:	colloidal silica, fumed silica, light anhydrous silicic acid, silicic anhydride and silicon dioxide fumed
Chemical Name	:	Silica
Molecular Weight	:	60.08
Structural Formula	:	SiO_2
Functional Category	:	Adsorbent, anticaking agent, emulsion stabilizer, glident, suspending agent, tablet disintegrant, thermal stabilizer, and viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Its small particle size and large specific surface area gives desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tabletting.

Description

Colloidal silicon dioxide is submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, and non-gritty amorphous powder.

Stability and Storage Conditions

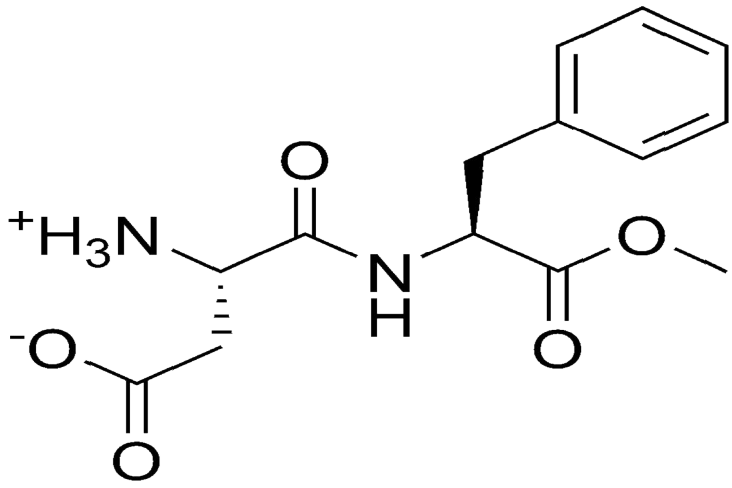
Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. However, at a pH greater than 7.5 the viscosity-increasing properties of colloidal silicon dioxide are reduced; and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates. Colloidal silicon dioxide powder should be stored in a well-closed container. Some grades of colloidal silicon dioxide have hydrophobic surface treatments that greatly minimize their hygroscopicity.

❖ **Aspartame** [79]

Non proprietary Names

BP	:	Aspartame
PhEur	:	Aspartame
USP-NF	:	Aspartame
Synonyms	**:**	aspartamum; aspartyl-L-phenylalaninate.
Chemical Name	**:**	N-L-α-Aspartyl-L- phenylalanine 1-methyl ester

Structural Formula



Empirical Formula and Molecular Weight

$C_{14}H_{18}N_2O_5$ 294.30

Description : Aspartame occurs as an off white, almost odourless crystalline powder with an intensely sweet taste.

Functional Category : Sweetening agent.

Applications in Pharmaceutical Technology

Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations. It enhances flavour systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180-200 times that of sucrose.

Plan of the Work

- ★ Characterization of API
- ★ To perform Pre-formulation studies
- ★ To develop and optimize the formula for Tramadol Hydrochloride ODT
- ★ Evaluation of Tramadol HCl ODT
    - * Thickness
    - * Hardness
    - * Friability test
    - * Disintegration time test
    - * Dispersion time test
    - * Drug content uniformity
    - * Dissolution study
    - * Assay
    - * Accelerated stability testing
    - * *Invivo* studies

6.1 Materials

Table 3 List of Materials used in the Study

Sl. No	Materials	Manufacturer/Suppliers
1	Tramadol HCl	KAPL, Banglore
2	β cyclodextrin	Roquette pharma, Germany
3	Microcrystalline cellulose	KAPL, Banglore
4	Crospovidone	KAPL, Banglore
5	Croscarmellose sodium	KAPL, Banglore
6	Sodium starch glycolate	KAPL, Banglore
7	Aspartame	KAPL, Banglore
8	Aerosol	KAPL, Banglore
9	Magnesium stearate	KAPL, Banglore
10	Talc	KAPL, Banglore
11	Mint flavour	KAPL, Banglore

Table 4 List of equipments

Sl. No	Materials	Manufacturer/Supplier
1	Electronic weighing balance	Mettler Toledo (Germany)
2	Compression Machine	Smart press SRC12i (Germany)
3	Hardness and Thickness tester	INWEKA Hardness tester (Germany)
4	Friabilator	Electrolab, EF-1W (USA)
5	Dissolution Apparatus USP – Type II	Electrolab ED-2 Type-II (USA)
6	FTIR	Shimadzu FTIR-8400S (Japan)
7	Hot Air Oven	NEWTRONIC HTA instrumentation (p) LTD (India)
8	UV Spectrometer	Shimadzu UV-1601pc (Japan)

6.2 Methods

6.2.1 *Pharmaceutical Buffer solutions*

6.2.1.1 0.1M Hydrochloric Acid (USP) [80]

50 ml potassium chloride in a 200 ml volumetric flask, add 85 ml of 0.2M Hydrochloric acid and then add water to volume.

6.2.1.2 Phosphate Buffer [81]

Place 50ml of 1M KH_2PO_4 in a 200 ml volumetric flask and mix 3.6 ml of 0.2M NAOH and dilute to volume with water.and pH was adjusted to 3.5 with ortho-phosphoric acid.

6.2.2 *Pre-formulation Studies*

It is one of the important prerequisite in development of any drug delivery system. A pre-formulation study concentrates on those physicochemical properties of the new compound that could affect drug performance and development of efficacious dosage form. It is the first step in the rational development of the drug formulation.

6.2.2.1 Melting Point

Melting point of Tramadol HCl was determined by capillary method. Fine powder of Tramadol HCl was filled in glass capillary tube (previously sealed on one end). The temperature at which the drug started melting was noted and recorded.

6.2.2.2 Assay

Weigh 50mg of tramadol hydrochloride and transferred to a 100ml volumetric flask; the volume was made-up with 0.1 N HCl and sonicated for 30 min to break the complex. The samples were filtered through Whattman filter paper No. 41, diluted suitably and absorbance was measured at 272 nm.

6.2.2.3 Preparation of Standard calibration curve of Tramadol Hydrochloride

I Stock solution: A weighed amount of the Tramadol hydrochloride (100mg) was taken and dissolved in 50ml of 0.1N hydrochloric acid and the volume was made up with 100ml of 0.1 HCl.

II Stock solution: From the I-stock solution 10ml was withdrawn and diluted to 50ml with 0.1N HCl to get a concentration of 200µg/ml. From standard stock solution-2 aliquots sample of 1ml, 2ml, 3ml, 4ml, 5ml and 6ml were pipetted into 10ml volumetric flasks. The volume was made up with 0.1 N HCl to get the final concentration of 20,40,60,80 and 100µg/ml respectively. The absorbance of each concentration was measured at 272 nm. From standard stock solution-2 aliquots sample of 1ml, 2ml, 3ml, 4ml, 5ml and 6ml were pipetted into 10ml volumetric flasks. The volume was made up with 0.1 N HCl to get the final concentration of 20,40,60,80 and 100µg/ml respectively. The absorbance of each concentration was measured at 272 nm.

6.2.2.4 Compatibility Studies by FTIR

Compatibility with polymers was confirmed by carrying out I R studies. The pure drug and its formulations along with excipients were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed.

6.2.3 *Taste Masking*

6.2.3.1 Inclusion Complex using β-cyclodextrin by Kneading Technique [82, 83]

A mixture of Tramadol HCl and β cyclodextrin was ground in a glass container and a minimum amount of water was added Add small quantity and triturated for 15-30min to get the slurry and air dried at 40^0c for 24hrs, pulvirised and passed through sieve no:100 and stored in a dessicator over fused $cacl_2$.

6.2.3.2 Estimation of Drug Content of Complex

An accurately weighed amount of Drug-inclusion complex (~100) was transferred to a 50ml volumetric flask; the volume was made-up with 0.1 N HCl and sonicated for 30 min to break the complex. The samples were filtered through Whattman filter paper No. 41, diluted suitably and absorbance was measured at 272 nm.

6.2.4 *Preparation of Tablets*

Step 1: Sifting of the drug and the excipients

Composition of tablets is mentioned in Table 5. All materials were passed through sieve no. 40.

Step 2: Disintegrant was divided into two equal parts by weight. Drug complex, one part of Superdisintegrant and aspartame.

Step 3: Mixing

The sifted step 1 materials were blended for 10mins.

Step 4: Sifting

Blended mass were sifted through 20/40 mesh screen. Ten percent of the fines were added to the mass and then blended for 2 minutes.

Step 5: Blending and Lubrication

A weighted quantity of Aerosil and remaining superdisintegrant were added to the mass and blended for five minutes.

Step 6: Compression

The granules of the drug were compressed in a 16 station rotary compression machine using flat faced punches of 10mm diameter.

Table 5 Composition of Oral Dispersible tablet of Tramadol HCl (All quantities in mg)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug complex	151.2	151.2	151.2	151.2	151.2	151.2	151.2	151.2	151.2
Micro crystalline cellulose	116.3	110.3	104.3	116.3	110.3	104.3	116.3	110.3	104.3
Crospovidone	12	18	24	_	_	_	_	_	_
Croscarmellose	_	_	_	12	18	24	_	_	_
Sodium starch glycolate	_	_	_	_	_	_	12	18	24
Aspartame	6	6	6	6	6	6	6	6	6
Aerosil	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Talc	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mint flavour	3	3	3	3	3	3	3	3	3
Total weight of the tablet	300	300	300	300	300	300	300	300	300

6.2.5 *Evaluation of Granules*

6.2.5.1 Bulk Density (D_b) [84, 85]

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured in to graduate measuring cylinder through large funnel and volume was measured, which is called initial bulk volume. It is expressed in gm/ml and is given by

$$D_b = M / V_0$$

where, M is the mass of powder.

V_0 is the bulk volume of the powder.

6.2.5.2 Tapped Density (D_t) [86]

Ten gram of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in gm/ml and is given by,

$$D_t = M / V_t$$

where, M is the mass of powder.

V_t is the tapped volume of the powder.

6.2.5.3 Flow Properties

Angle of repose, compressibility index and Hausner ratio were evaluated as per methods described in USP 30-NF25.

6.2.5.3.1 Angle of Repose [86, 87]

For determining angle of repose a funnel was mounted on a stand at a fixed height and a fix weighed quantity of each blend was poured through the funnel. The

height and the base diameter of the pile was noted and angle of repose was calculated as

Angle of repose = $\tan^{-1}$ (height/ 0.5 base)

Table 6 Flow Properties Corresponding to Angle of Repose

Flow character	Angle of repose (degrees)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable-may hang up	41-45
Poor	46-55
Very poor	56-65
Very, very poor	>66

6.2.5.3.2 Compressibility Index and Hausner's Ratio[84]

In the recent years compressibility index and the closely related Hausner ratio have become the simple, fast and popular methods of predicting powder flow characteristics. The basic procedure to calculate the compressibility index and Hausner ratio involves measuring the bulk volume (V_0) and final tapped volume (V_f). A 250 ml volumetric cylinder with 100 gm of the material is used for this purpose. The calculations are done as:

Compressibility index = $100 (V_f - V_0) / V_f$

Hausner ratio = $(V_f) / V_0$

Table 7 Flow Properties Corresponding to Compressibility Index and Hausner Ratio

Flow character	Compressibility index (%)	Hausner ratio
Excellent	<10	1.00-1.11
Good	11-15	1.12-1.18
Fair	16-20	1.19-1.25
Passable	21-25	1.26-1.34
Poor	26-31	1.35-1.45
Very poor	32-37	1.46-1.59
Very, very poor	>38	>1.60

6.2.6 *Evaluation of Oral Dispersible Tablets*

6.2.6.1 General Appearance and Organoleptic Properties

The control of a general appearance of a tablet involves the measurement of a number of attributes such as a tablet's size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws and consistency, and legibility of any identifying markings.

6.2.6.2 Shape, Thickness and Dimension[85]

Six tablets from each batch were selected and measured for thickness and diameter using digital vernier calipers. The extent to which the thickness of each tablet deviated from ± 5% of the standard value was determined.

6.2.6.3 Hardness

Five tablets from each batch were selected and hardness was measured using Monsanto hardness tester to find the average tablet hardness.

6.2.6.4 Friability (%F) [85]

20 tablets from each batch were selected randomly and weighed. These tablets were subjected to friability testing using Roche friabilator for 100 revolutions. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the % friability

%F =1-(loss in weight/ initial weight) 100

6.2.6.5 Weight Variation[88]

Weight variation was calculated as per method descried in Indian Pharmacopoeia (I.P. 1996). 20 tablets were weighed individually and the average weight was calculated. The requirements are met if the weights of not more than 2 tablets differ by more than the percentage listed in Table and no tablets differ in weight by more than double that percentage.

Table 8 Weight Variations Allowed as per I.P. 1996

Average weight of tablet (mg)	Percentage difference allowed
80 mg or less	10
More than 80 mg but less that 250 mg	7.5
250 mg or more	5

6.2.6.6 Drug Content

Finely powder not fewer than 20 tablets. Transfer a portion of the powder, equivalent to 50mg of tramadol hydrochloride, and transferred to a 100ml volumetric flask; the volume was made-up with 0.1 N HCl and sonicated for 30 min to break the complex. The samples were filtered through Whattman filter paper No. 41, diluted suitably and absorbance was measured at 272 nm.

6.2.6.7 Disintegration Time[88]

The in-vitro disintegration time was determined by using disintegration test apparatus. One tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass in the apparatus was measured in seconds.

6.2.6.8 Wetting Time

A Petri dish containing 6 ml of distilled water was used. A tissue paper folded twice was kept in the dish and a tablet was placed on it. A small quantity of amaranth red color was put on the upper surface of the tablet. Time required for the upper surface of the tablet to become red was noted as the wetting time of the tablet.

6.2.6.9 Dissolution Studies

The *In vitro* dissolution test was carried out using USP Type II dissolution test apparatus at 37±2°C and 50 rpm speed. 900 ml of 0.1 N HCl was used as dissolution medium. Aliquot equal to 10 ml was withdrawn at specific time intervals and amount of Tramadol released from tablet was determined.

6.2.7 *Release Kinetics*

The results of *In-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows.

1. Log cumulative percent drug remaining versus time (first order kinetic model)
2. Cumulative percent drug release versus square root of time (Higuchis model)
3. Cumulative percent drug release versus time (zero order kinetic model)
4. Log cumulative Percent Drug released versus log time (korsmeyers model)

6.2.7.1 Drug Release Kinetics-model Fitting of the Dissolution Data [89 -91]

Whenever a new solid dosage form is developed or produces, it is necessary to ensure that drug dissolution occurs in an appropriate manner. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q = f (t). Some analytical definitions of the Q (t) function are commonly used such as zero order, first order, Higuchi, korsmeyers-peppas models. Other release parameters, such as dissolution time ($t_{x\%}$), dissolution efficacy (ED), difference factor (f_1), similarity factor (f_2) can be used to characterize drug dissolution / release profile.

1. Zero-order Kinetics

A zero-order release would be predicted by the following equation.

$$\mathbf{At = A_o - K_o t} \qquad (1)$$

where,

At = Drug release at time t

A_o = Initial drug concentration

K_o = Zero-order rate constant (hr)

When the data is plotted as cumulative percent drug release versus time if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to k_o.

Use: This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in case of some transdermal systems etc. the pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a prolonged pharmacological action.

2. First-order Kinetics

A first order release would be predicted by the following equation.

$$\text{Log } C = \text{Log } Co - Kt / 2.303 \quad (2)$$

where

C = Amount of drug remained at time t

C_o = Initial amount of drug

K = First-order rate constant

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line indicating the release follows first-order kinetics, the constant k can be obtained by multiplying 2.303 with slope values

Use: The pharmaceutical dosage forms containing water-soluble drugs in porous matrices, follows this type of dissolution profile. The release of the drug is proportional to the amount of drug remaining in its interior so that the amount of drug release by unit of time diminishes

3. Higuchi Model

Drug release from the matrix devices by diffusion has been described by following higuchis classical diffusion equation.

$$\mathbf{Q = [DE/ \tau(2A- ECs) C_{st}]} \quad (3)$$

where

Q = Amount of drug release at time t

D = Diffusion coefficient of the drug in the matrix

A = Total amount of drug in unit volume of matrix

C_s = The solubility of the drug in the matrix

E = Porosity of the matrix

T = Time in hrs at which q is the amount of drug is release

Equation-3 may be simplified if one assumes that D, Cs and A are constant. Then equation-3 becomes

$$\mathbf{Q = K_t ½}$$

When the data is plotted according to equation-4 i.e. cumulative drug release versus Square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to k.

Use: The relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in case of some water soluble drugs.

4. Korse Meyer Peppas Model

In order to understand the mode of release of drug from swellable matrices, the data were fitted to the following equation

$$\mathbf{M_t / M_{\acute{\alpha}} = Kt^n}$$

where,

$M_t / M_{\acute{\alpha}}$ = the fraction of drug released at time 't'

K = Constant incorporating the structural and geometrical Characteristics of the drug / polymer system.

n = Diffusion exponent related to the mechanism of release.

The above equation can be simplified by applying log on both sides we get

$$\mathbf{Log\ M_t / M_{\acute{\alpha}} = Log\ K + n\ Log\ t}$$

When the data is plotted as a log of drug released versus log time, yields a straight line with a slope equal to n and the k can be obtained from y- intercept.

The value of n for a cylinder is <0.45 for fickian release, > 0.45 and < 0.89 for non-fickian release, 0.89 for the case 2 release and > 0.89 for super case2 type release.

6.2.8 *Stability Studies*

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions and shelf lives to be established.

In the present study, the stability studies were carried out as per ICH guidelines $40^0C \pm 2^0C$ / 75% ± 5% RH for the following selected formulation for 1 month.

Formulation F3

After specified time intervals, parameters like physical appearance, disintegration time, drug content, and dissolution were evaluated according to the procedure described as earlier.

6.2.9 *In vivo Studies* [92, 93]

Animals: Healthy adult rabbits. (Approval number: IAEC/XXXIV/05/CLB MCP/2011 dated 07.12.2011)

Procedure: Physical examinations and plasma biochemical analyses were performed to ensure rabbits were healthy prior to the experiment. One blood sample was collected before treatment with tramadol through marginal ear vein. Then, tramadol was administered once, and blood samples were collected at various time points up to 6hrs after administration. Blood samples were analyzed with high-performance liquid chromatography to determine plasma concentrations of tramadol.

Preparation of mobile phase, stock solution and plasma extraction method for HPLC analysis:

The mobile phase comprises of phosphate buffer (potassium dihydrogen phosphate 50mM) and its pH was adjusted to 3.5 using ortho-phosphoric acid. Then methanol and acetonitrile were added to the buffer solution containing 0.1% triethly amine. The mobile phase was sonicated and filtered through vacuum filter assembly by using cellulose acetate filter (0.45_m). A stock solution was prepared by dissolving 100mg of Tramadol hydrochloride in 100mLof methanol. Working solutions were prepared in methanol by appropriate dilutions of stock solution. All the solutions were stored at-20^0c and protected from light.

To 0.5mL of plasma, 500 ng of Tramadol hydrochloride (dissolved in 0.5mL distilled water) was added and vortexed for 2min. Methanol (2 mL) was added to the plasma to precipitate plasma proteins and again vortexed for 1 min. The final solution was subjected to centrifugation at 45,000rpm for 10 min. The

supernatant liquid was filtered and transferred to epindroff tube for injecting in HPLC port. Chromatographic separation was performed at ambient temperature on ODS hypersil C18 stainless steel analytical column, 5µm pore size, 4.6mm×250mm and Guard Column.

Results

Table 9 Raw Material Analysis of Tramadol Hydrochloride

S. No	Test	Observation
1	Melting point	183^0C
2	Solubility	Water, Methanol
3	Assay	99.72%

Determination of Drug Content

When Drug complex was prepared using all of the optimized parameters for drug loading, the percent drug loading was found to be 99.20% and hence the drug content was 49.60% w/w.

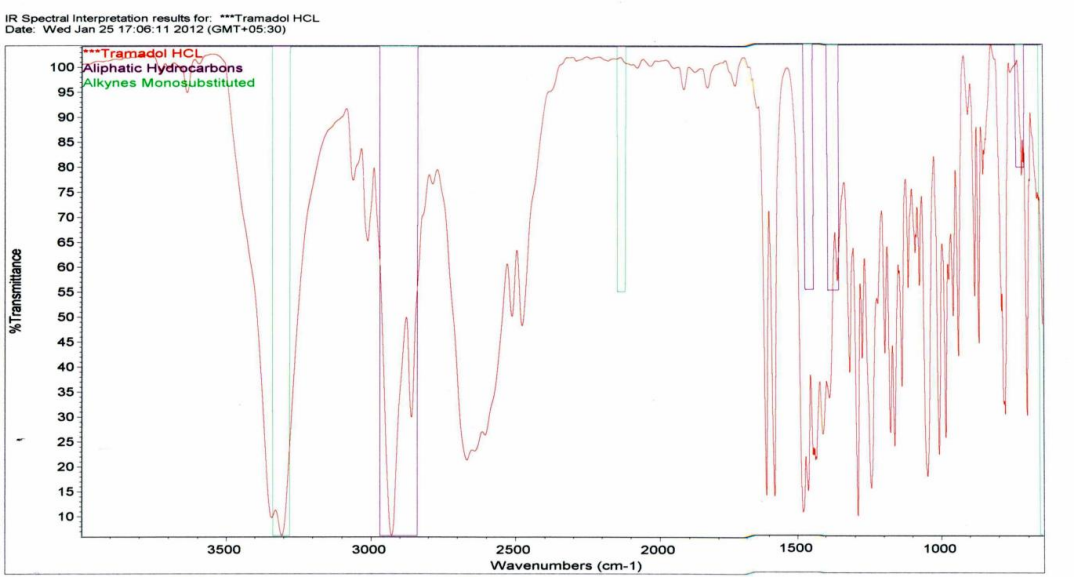


Fig. 4 FTIR Spectrum of Tramadol HCl

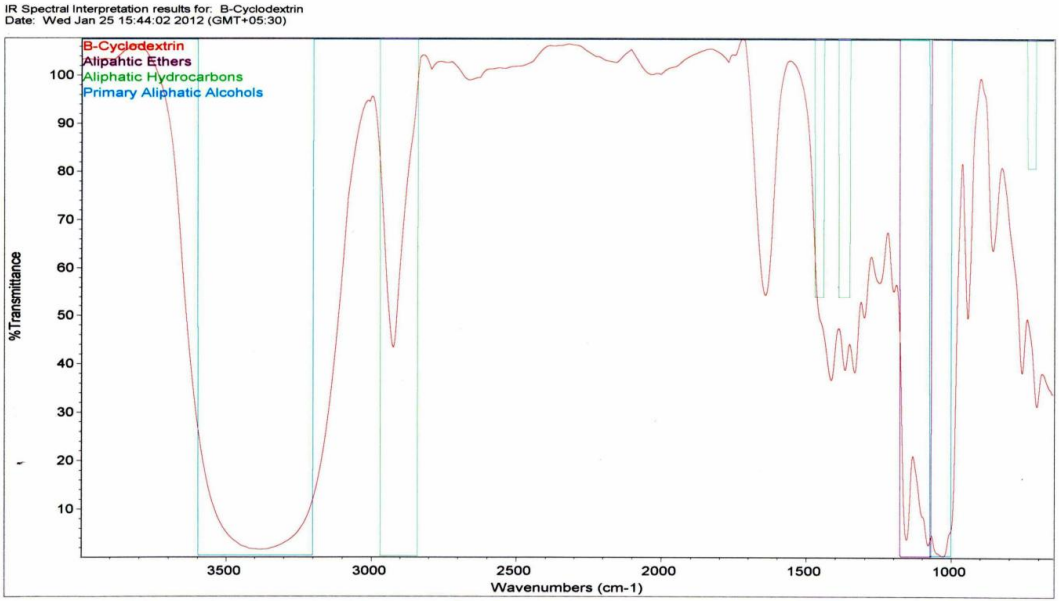


Fig. 5 FTIR Spectrum of β-cyclodextrin

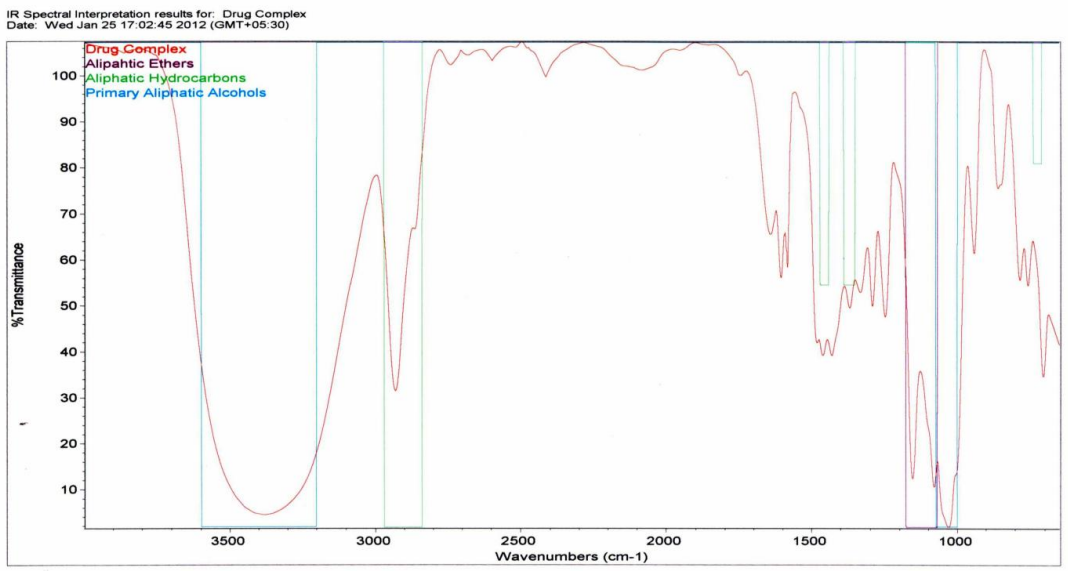


Fig. 6 FTIR Spectrum of Drug Complex

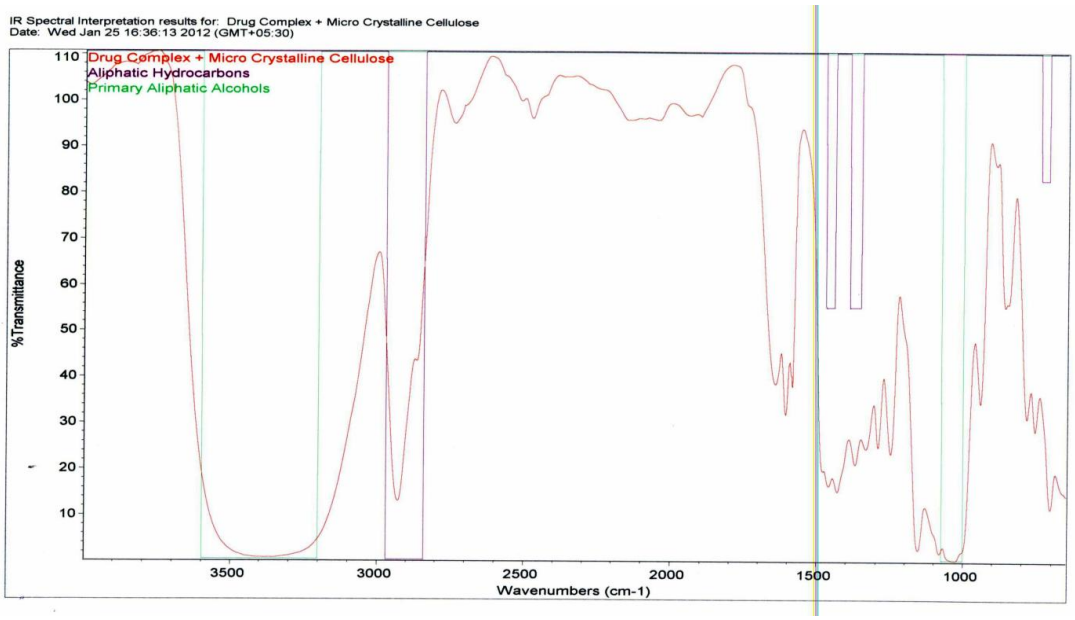


Fig. 7 FTIR Spectrum of Drug Complex with MCC

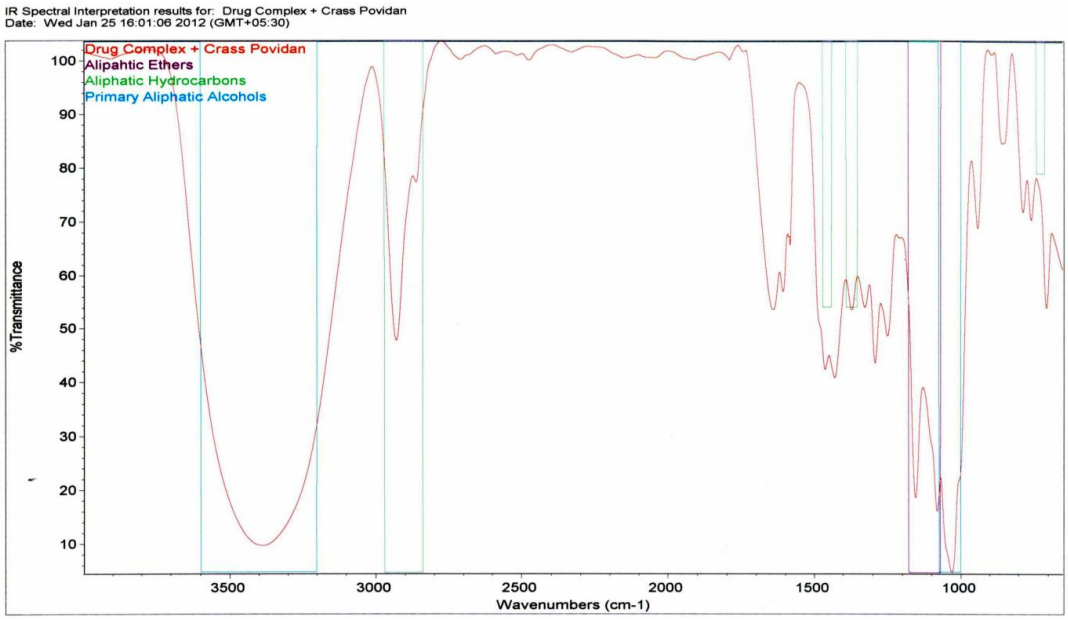


Fig. 8 FTIR Spectrum of Drug Complex with Crospovidone

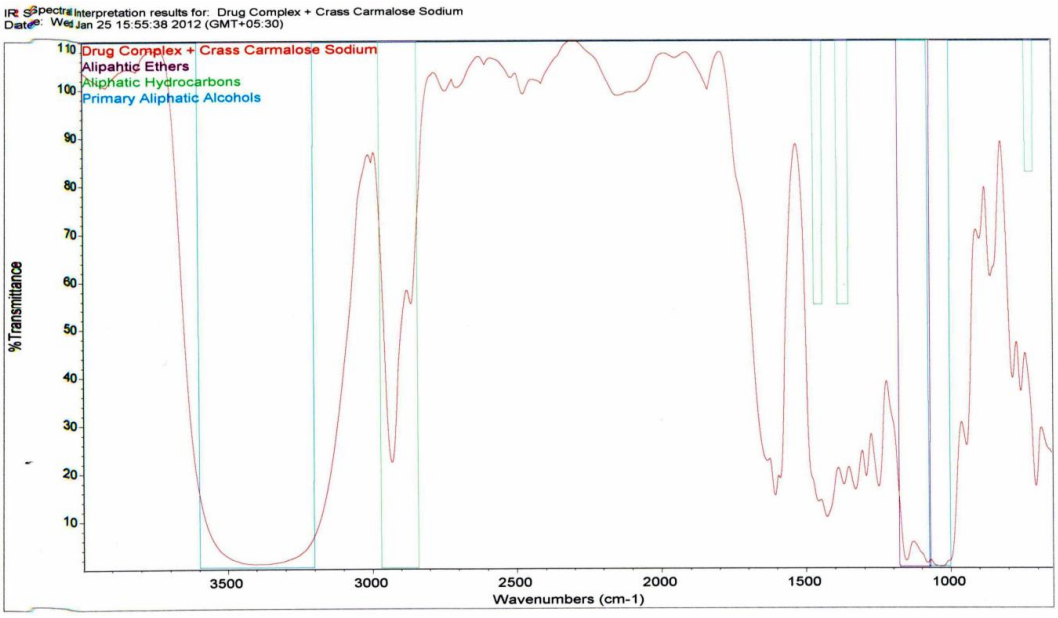


Fig. 9 FTIR Spectrum of Drug Complex with Cros Carmellose Sodium

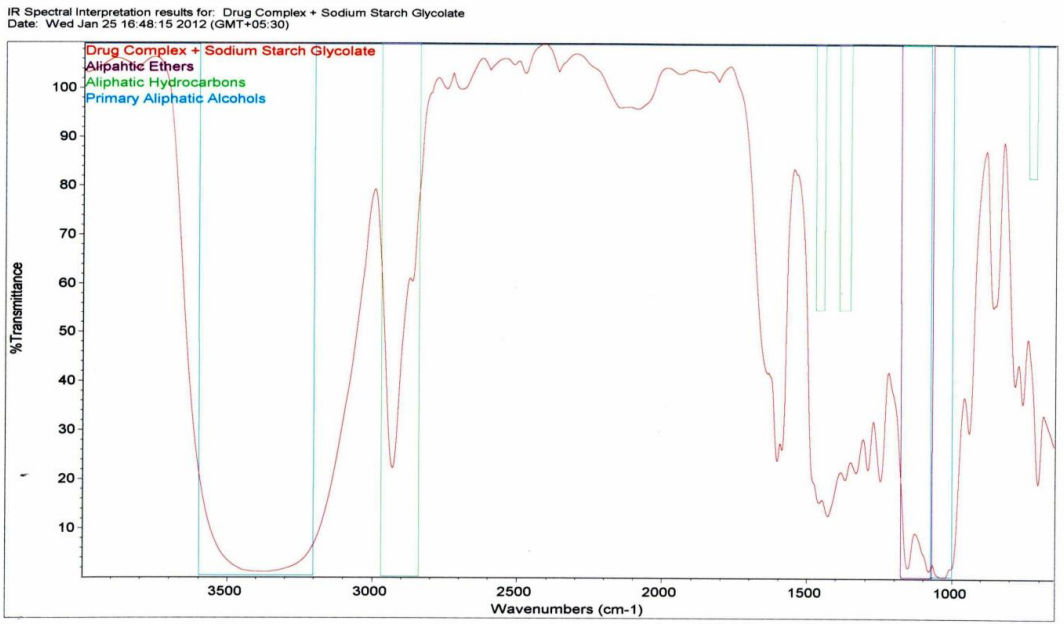


Fig. 10 FTIR Spectrum of Drug Complex with SSG

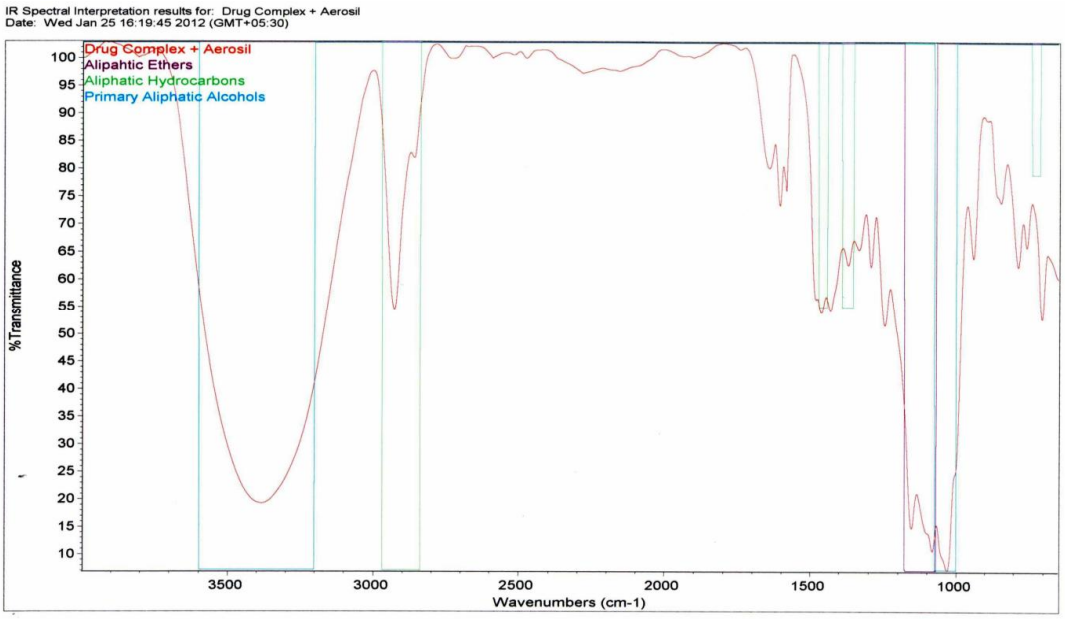


Fig. 11 FTIR Spectrum of Drug Complex with Aerosil

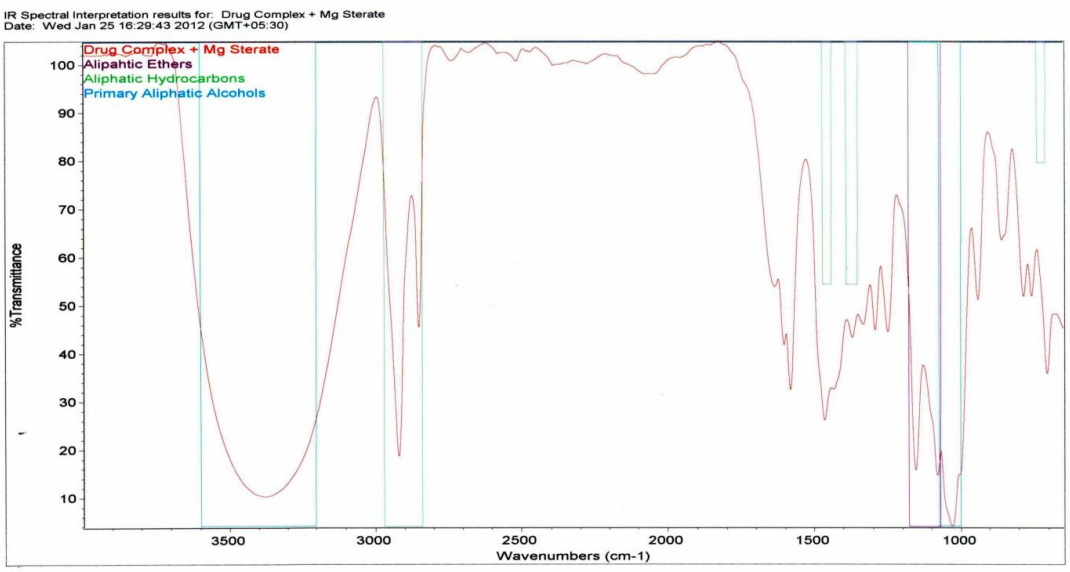


Fig. 12 FTIR Spectrum of Drug Complex with Magnesium Stearate

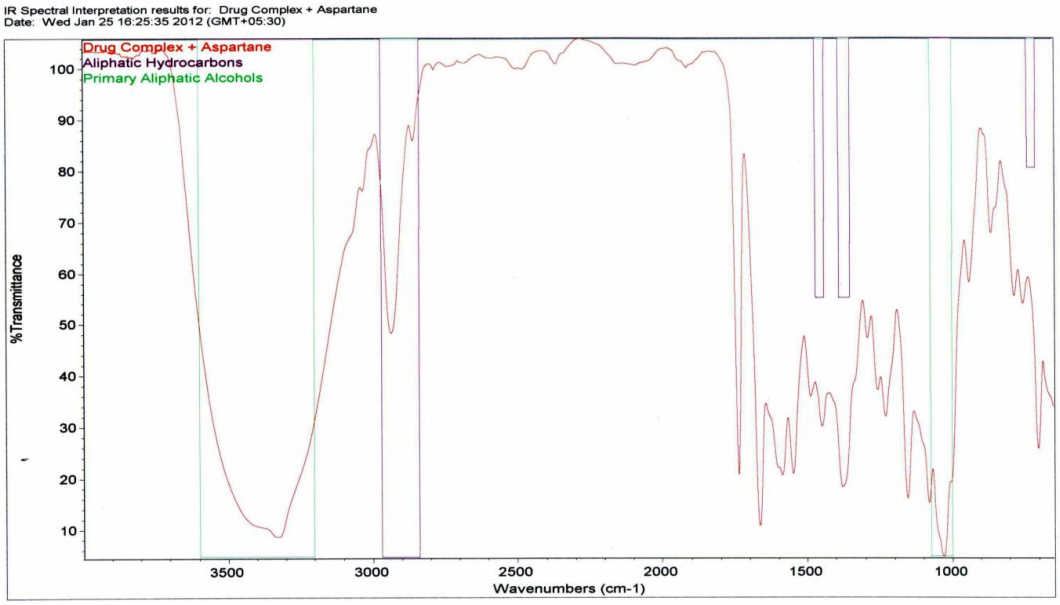


Fig.13 FTIR Spectrum of Drug Complex with Aspartame

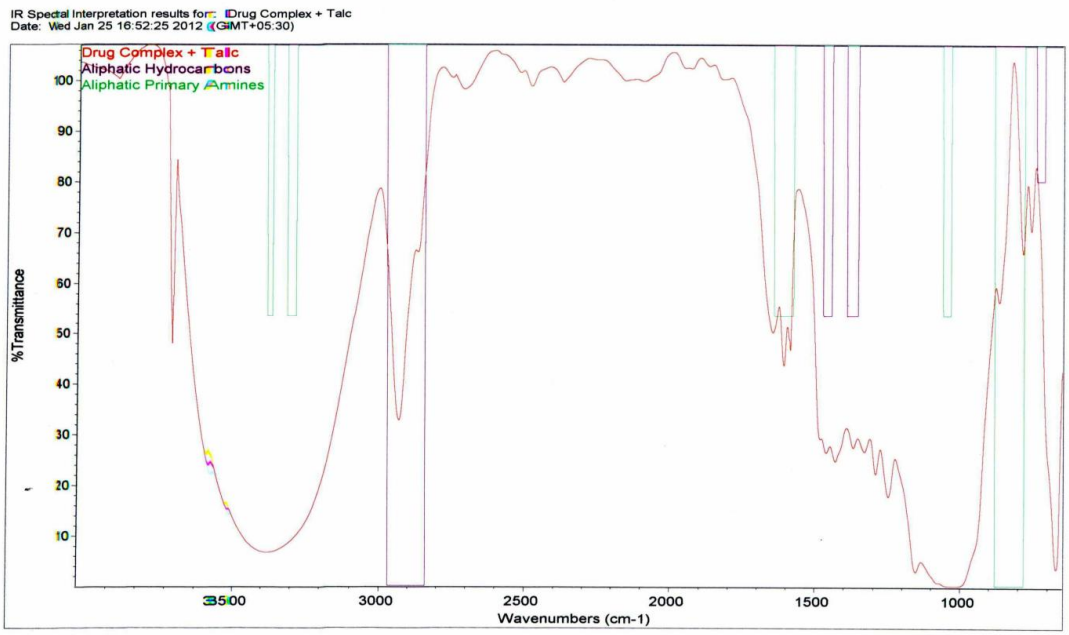


Fig.14 FTIR Spectrum of Drug Complex with Talc

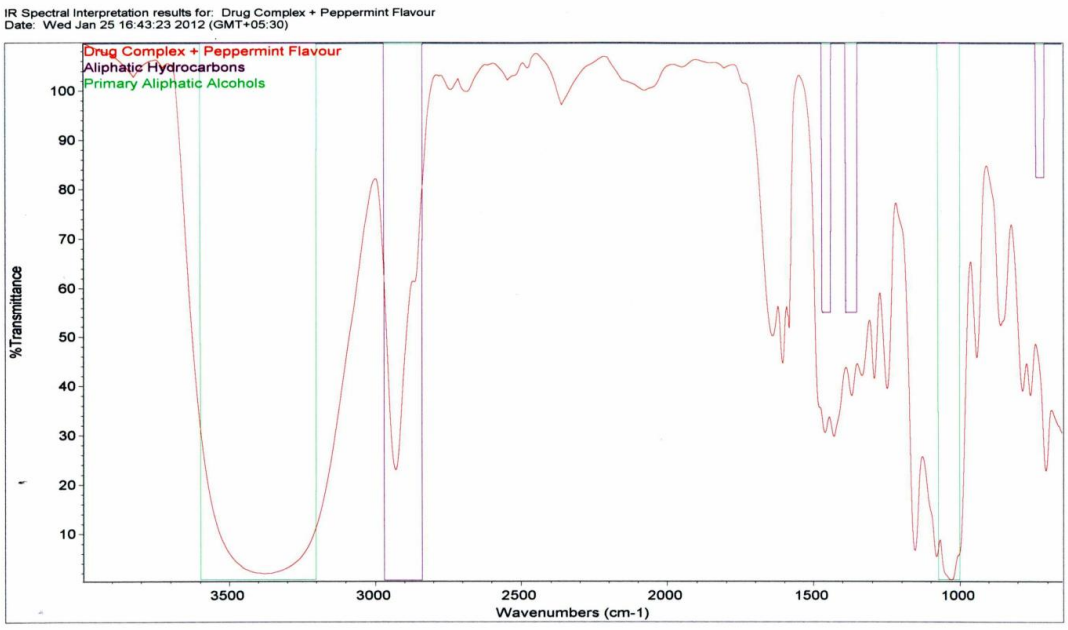


Fig.15 FTIR Spectrum of Drug Complex with flavour

Table 10 Standard calibration curve of Tramadol Hydrochloride using pH 1.2 Buffer (0.1M HCl)

S.No	Concentration (µg/ml)	Absorbance (nm)
1	0	0.000
2	20	0.126
3	40	0.262
4	60	0.366
5	80	0.484
6	100	0.611

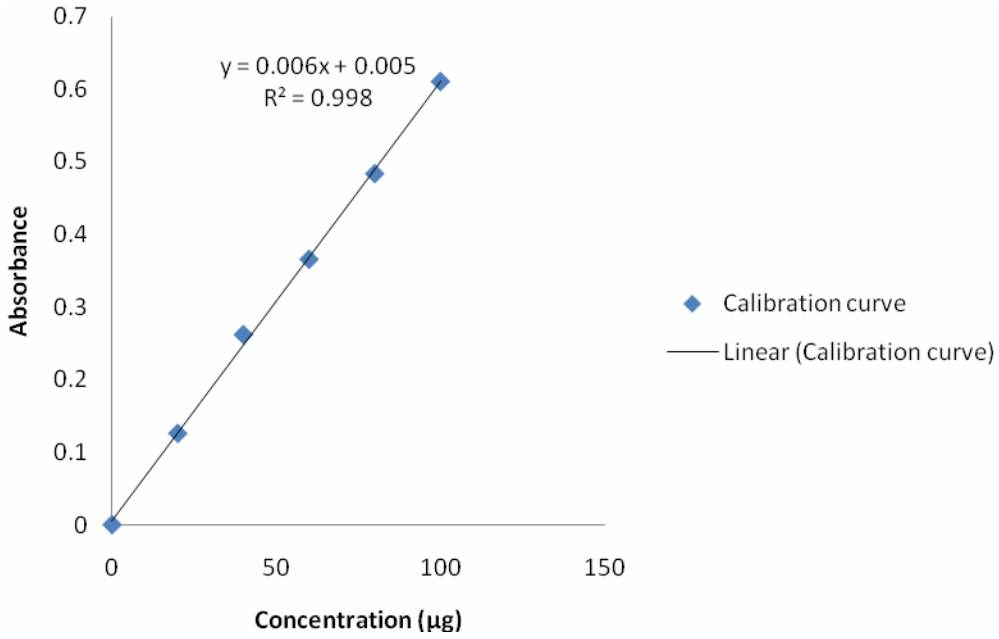


Fig. 16 Standard Calibration Curve of Tramadol Hydrochloride using pH 1.2 Buffer (0.1M HCl)

Table 11 Evaluation of precompressed granules of Tramadol HCl

Formulation	Bulk density (gm/cc) ±SD	Tapped density (gm/cc) ±SD	Compressibility index (%) ±SD	Hausner's ratio (%)±SD	Angle of repose(□) ±SD
F1	0.289±0.023	0.344±0.03	13.47±0.002	1.155±0.04	21.98±0.03
F2	0.309±0.021	0.348±0.012	11.02±0.03	1.126±0.01	20.43±0.04
F3	0.296±0.012	0.321±0.02	7.78±0.001	1.084±0.03	19.69±0.02
F4	0.293±0.023	0.316±0.023	7.27±0.012	1.078±0.01	20.79±0.05
F5	0.312±0.032	0.375±0.012	16.80±0.023	1.201±0.02	22.31±0.04
F6	0.295±0.014	0.342±0.021	13.74±0.023	1.159±0.31	21.01±0.21
F7	0.307±0.032	0.370±0.021	17.02±0.001	1.205±0.01	22.24±0.04
F8	0.281±0.041	0.324±0.012	13.27±0.001	1.153±0.02	19.76±0.03
F9	0.318±.021	0.347±0.024	8.35±0.002	1.091±0.03	21.47±0.05

Table 12 Evaluation of Compressed Granules of Tramadol Hydrochloride

Formulation	Weight Variation	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
F1	299±0.14	3.48±0.12	3.62± 0.016	0.462
F2	305±0.25	5.65±0.11	3.14±0.012	0.501
F3	301±0.01	4.53±0.14	3.42±0.01	0.442
F4	305±0.43	3.51±0.12	4.14±0.14	0.364
F5	304±0.38	4.21±0.14	3.27±0.03	0.409
F6	302±0.24	4.04±0.15	4.01±0.02	0.486
F7	298±0.18	4.79±0.14	3.93±0.12	0.423
F8	304±0.16	4.23±0.16	3.76±0.01	0.412
F9	306±0.41	4.54±0.13	4.15±0.13	0.389

Table 13 Evaluation of Compressed Granules of Tramadol Hydrochloride

Formulation	Wetting Time (sec)	Disintegrating Time (sec)	Drug content (%)
F1	75	31	98.23
F2	41	24	98.76
F3	23	18	99.12
F4	29	20	101.76
F5	30	27	100.14
F6	35	29	98.99
F7	29	32	99.01
F8	31	27	98.66
F9	27	26	98.41

Table 14 *Invitro* Dissolution Profile of Tramadol HCl from ODTs (F1)

S.No	Time (min)	cumulative % drug release ± SD
1	5	63.87±0.48
2	10	71.12±0.32
3	15	82.93±0.56
4	20	91.47±0.21
5	30	98.88±0.18

All values are expressed as mean ± SD, n=3

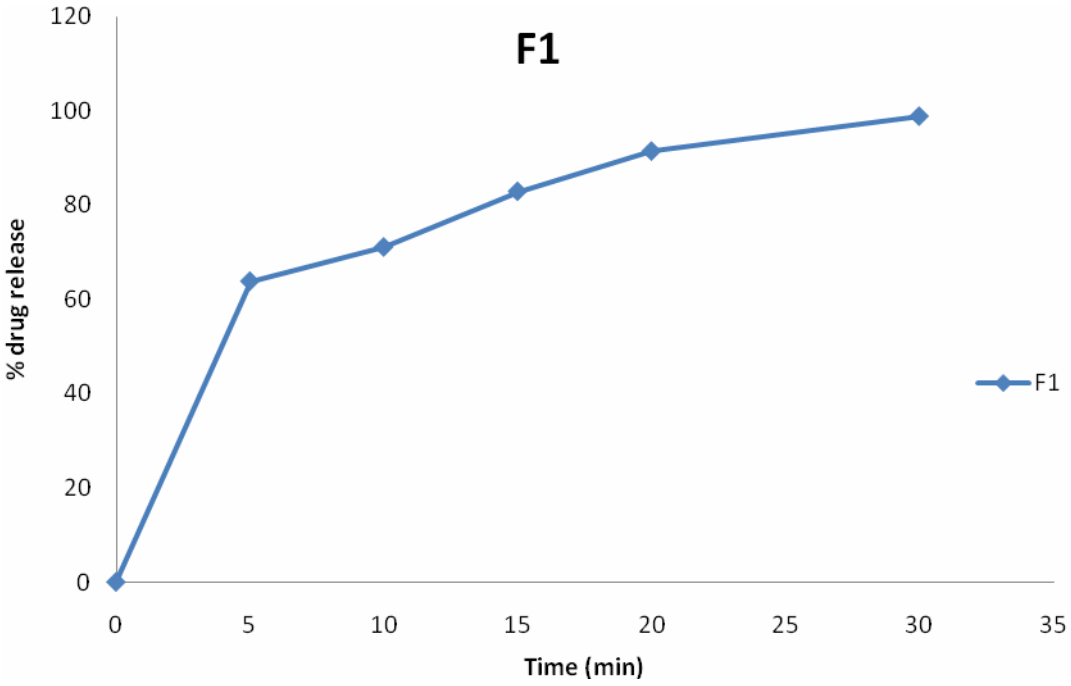


Fig. 17 *Invitro* Dissolution Profile of Tramadol HCl from ODTs (F1)

Table 15 *Invitro* Dissolution Profile of Tramadol HCl from ODTs (F2)

S.No	Time (min)	cumulative % drug release ± SD
1	5	67.31±0.42
2	10	74.02±0.12
3	15	82.35±0.41
4	20	90.20±0.23
5	30	97.15±0.32

All values are expressed as mean ± SD, n=3

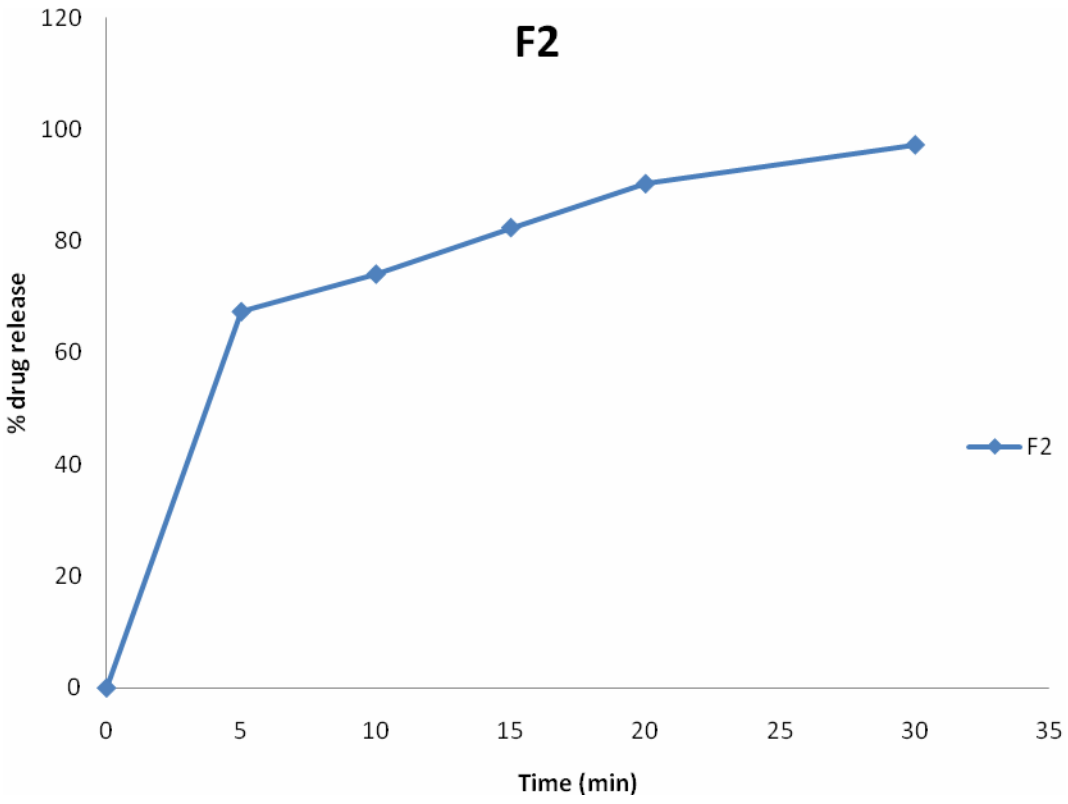


Fig. 18 *Invitro* Dissolution Profile of Tramadol HCl from ODTs (F2)

Table 16 *Invitro* Dissolution Profile of Tramadol HCl from ODTs (F3)

S.No	Time (min)	cumulative % drug release ± SD
1	5	61.05±0.16
2	10	69.66±0.12
3	15	78.11±0.32
4	20	90.29±0.21
5	30	99.18±0.18

All values are expressed as mean ± SD, n=3

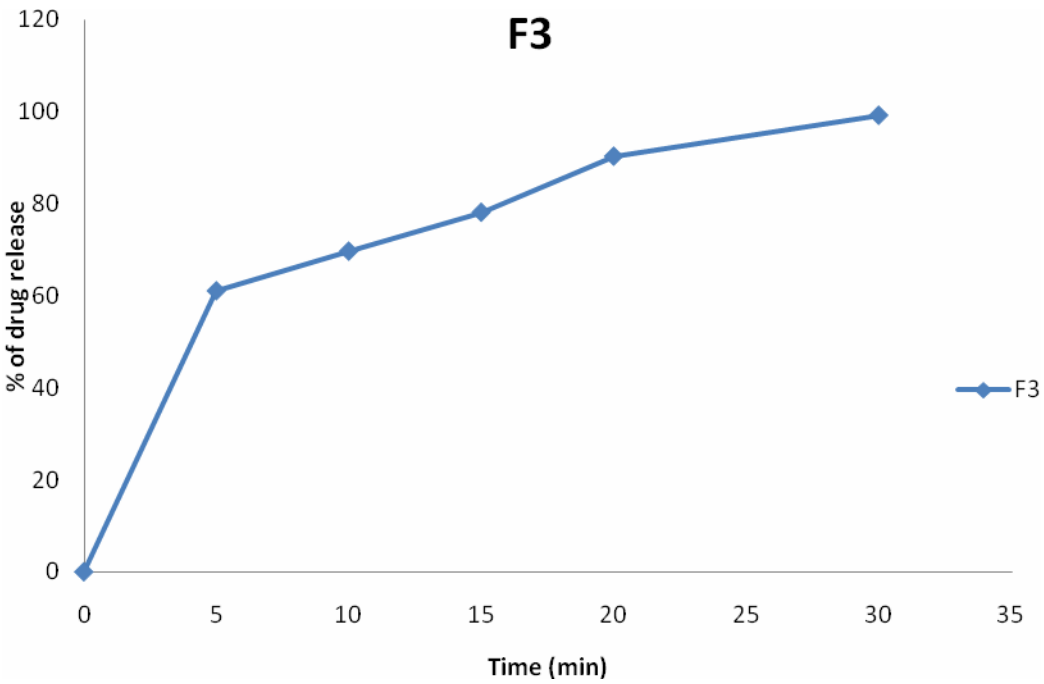


Fig. 19 *Invitro* dissolution profile of Tramadol HCl from ODTs (F3)

Table 17 *Invitro* dissolution profile of Tramadol HCl from ODTs (F4)

S.No	Time (min)	cumulative % drug release ± SD
1	5	65.81±0.32
2	10	74.42±0.12
3	15	82.32±0.16
4	20	89.38±0.21
5	30	94.87±0.18

All values are expressed as mean ± SD, n=3

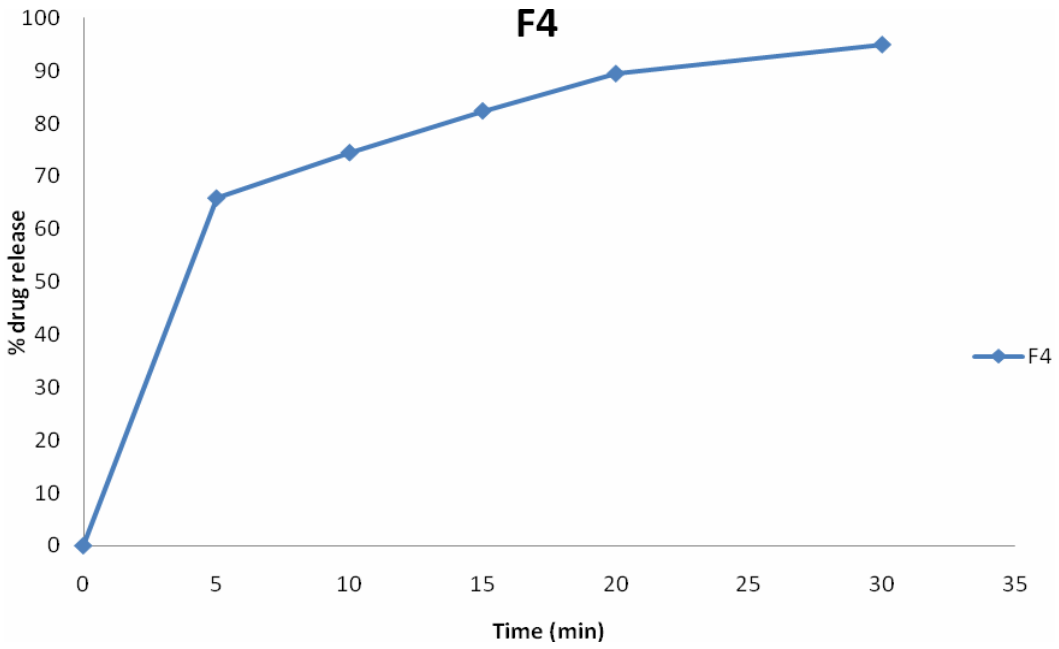


Fig. 20 *Invitro* Dissolution Profile of Tramadol HCl from ODTs (F4)

Table 18 *Invitro* Dissolution Profile of Tramadol HCl from ODTs (F5)

S.No	Time (min)	cumulative % drug release ± SD
1	5	59.11±0.21
2	10	67.15±0.16
3	15	76.10±0.23
4	20	87.21±0.12
5	30	96.74±0.34

All values are expressed as mean ± SD, n=3

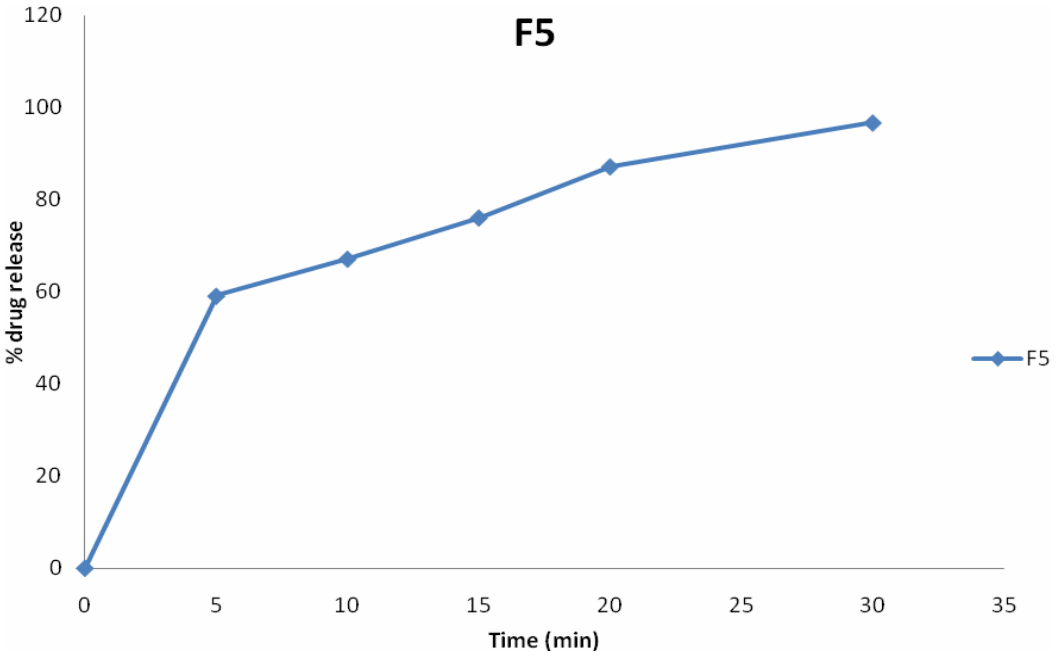


Fig. 21 *Invitro* Dissolution Profile of Tramadol HCl from ODTs (F5)

Table 19 *Invitro* Dissolution Profile of Tramadol HCl from ODTs (F6)

S.No	Time (min)	cumulative % drug release ± SD
1	5	67.89±0.16
2	10	74.92±0.32
3	15	85.83±0.21
4	20	90.58±0.23
5	30	97.54±0.14

All values are expressed as mean ± SD, n=3

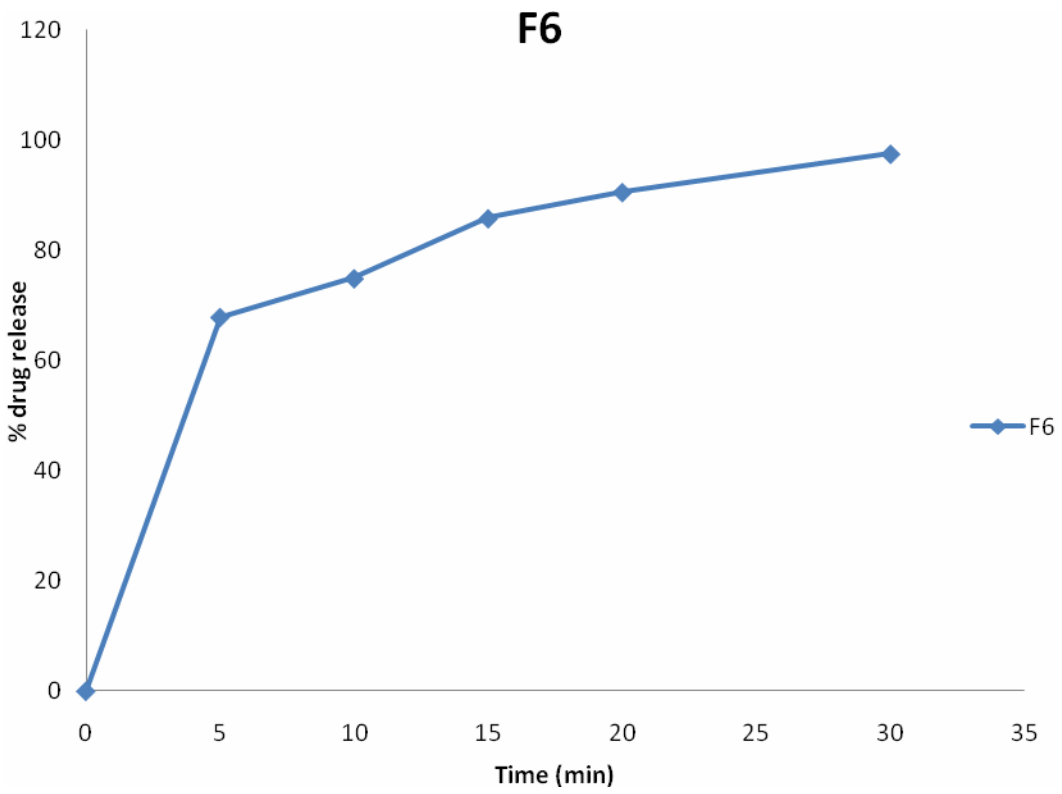


Fig. 22 *Invitro* Dissolution Profile of Tramadol HCl from ODTs (F6)

Table 20 *Invitro* Dissolution Profile of Tramadol HCl from ODTs (F7)

S.No	Time (min)	cumulative % drug release ± SD
1	5	68.71±0.16
2	10	75.45±0.25
3	15	81.06±0.13
4	20	92.84±0.21
5	30	98.42±0.33

All values are expressed as mean ± SD, n=3

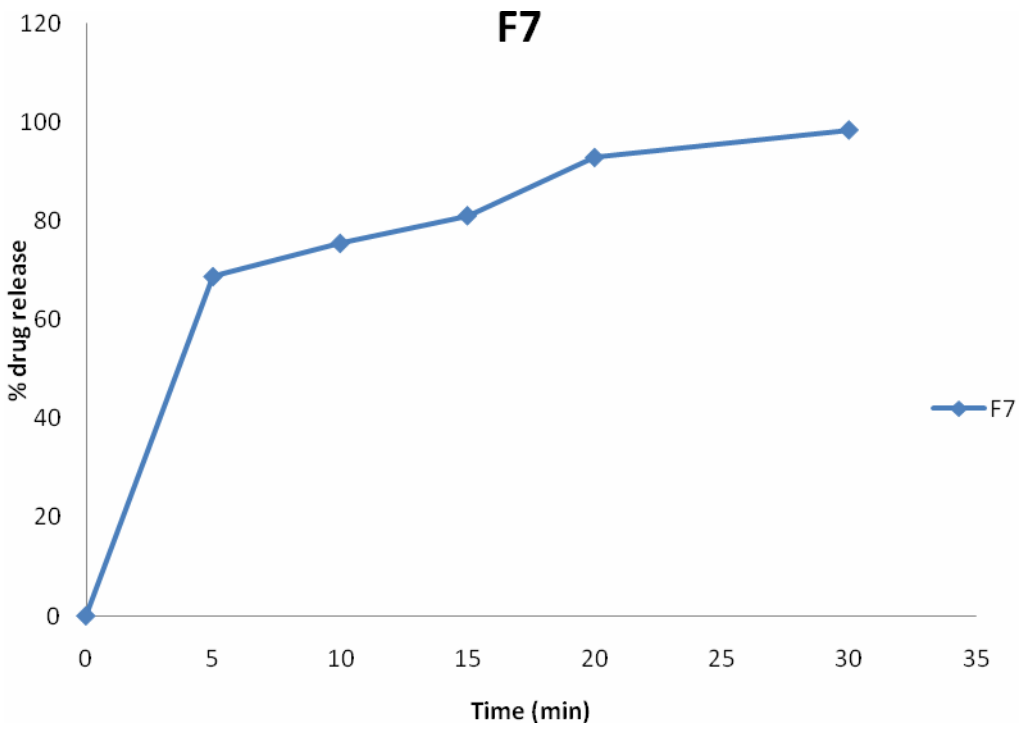


Fig. 23 *Invitro* Dissolution Profile of Tramadol HCl from ODTs (F7)

Table 21 *Invitro* Dissolution Profile of Tramadol HCl from ODTs (F8)

S.No	Time (min)	cumulative % drug release ± SD
1	5	72.49±0.23
2	10	81.62±0.21
3	15	88.51±0.33
4	20	94.96±0.14
5	30	97.21±0.17

All values are expressed as mean ± SD, n=3

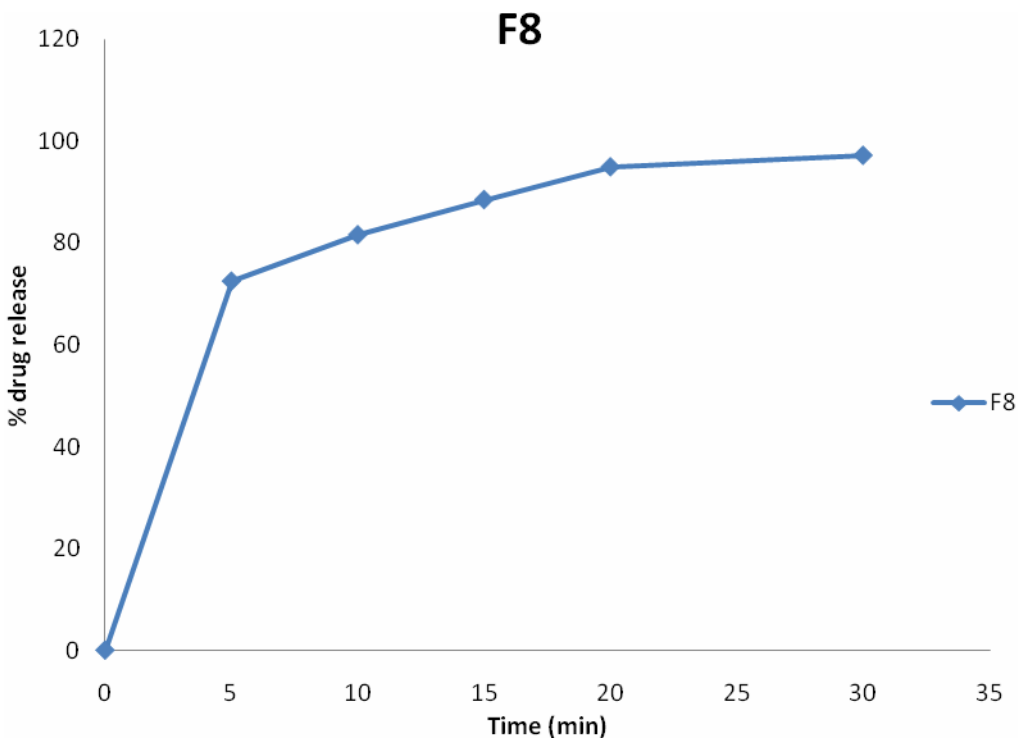


Fig. 24 *Invitro* Dissolution Profile of Tramadol HCl from ODTs (F8)

Table 22 *Invitro* Dissolution Profile of Tramadol HCl from ODTs (F9)

S.No	Time (min)	cumulative % drug release ± SD
1	5	69.11±0.42
2	10	77.83±0.32
3	15	84.83±0.21
4	20	91.59±0.17
5	30	97.86±0.25

All values are expressed as mean ± SD, n=3

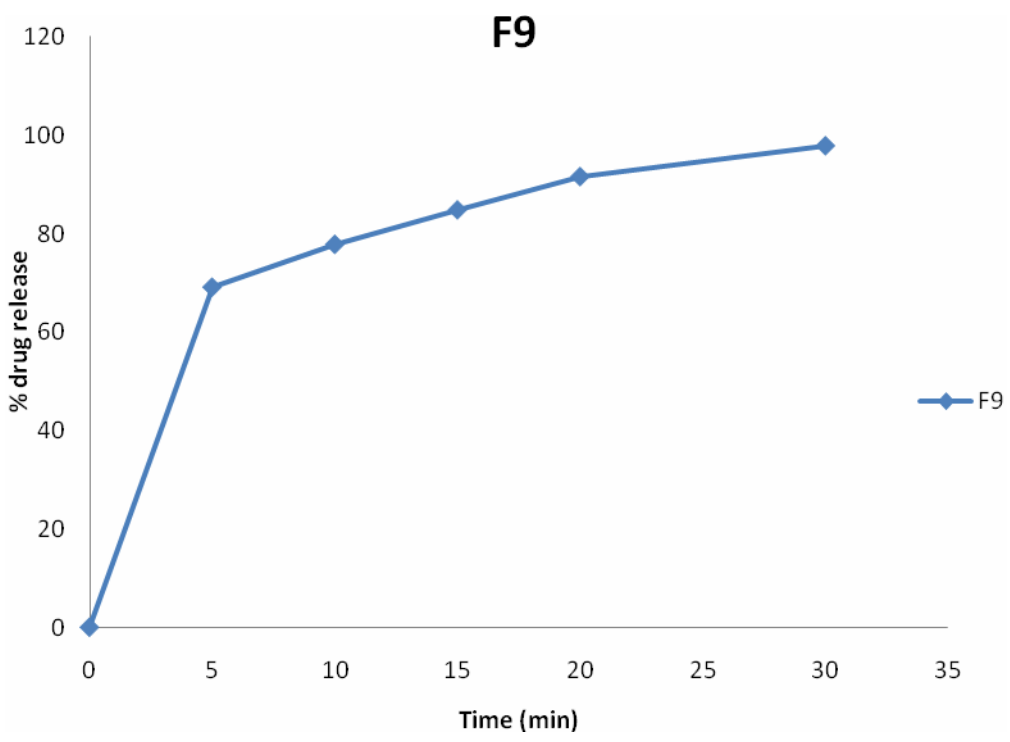


Fig. 25 *Invitro* Dissolution Profile of Tramadol HCl from ODTs (F9)

Determination of Release Kinetics:

Table 23 Kinetic Studies of Oral Dispersible Tablets

Release kinetics	R^2	Intercept	Slope
Zero order	0.971	54.48	1.573
First order	0.908	2.142	0.067
Higuchi	0.982	32.33	12.31
Korsmeyer peppas	0.972	1.577	0.280

Dissolution- Zero Order Kinetics

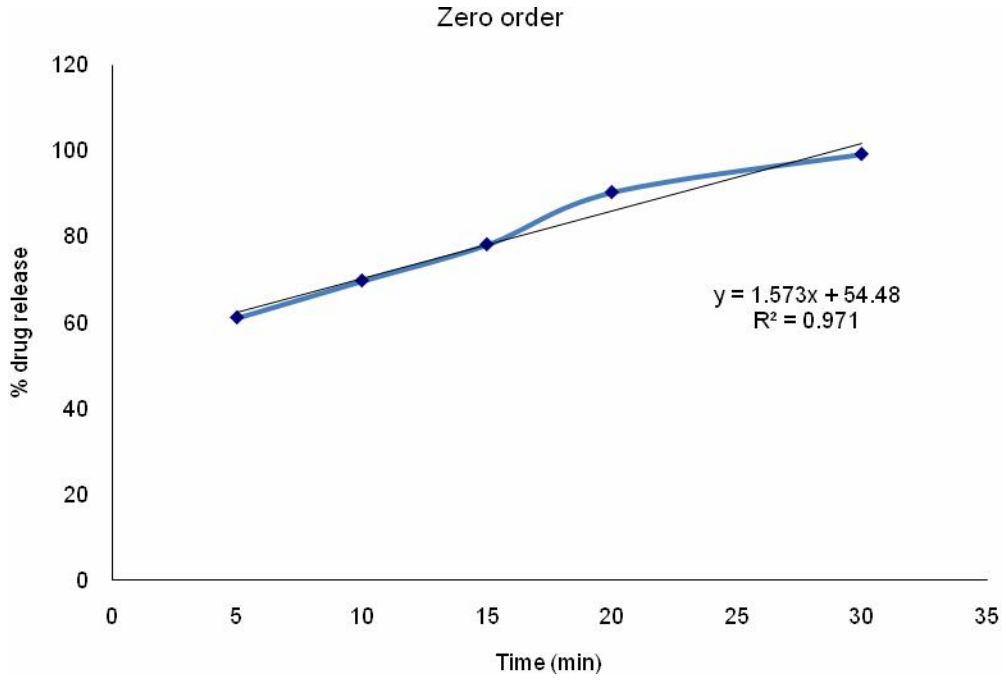


Fig. 26 Graph for the Formulation F3-Zero Order Kinetics

Dissolution- First Order Kinetics

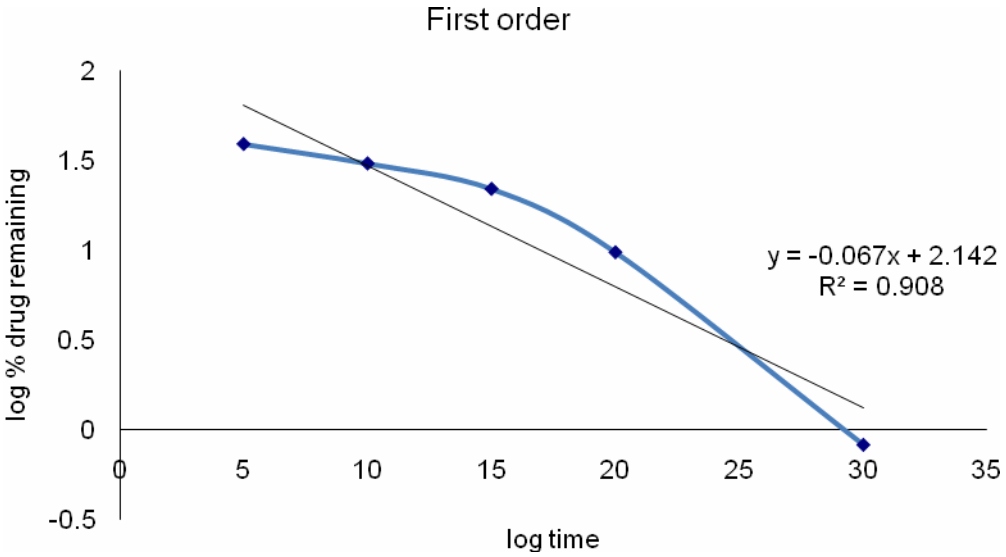


Fig. 27 Graph for the Formulation F3-First Order Kinetics

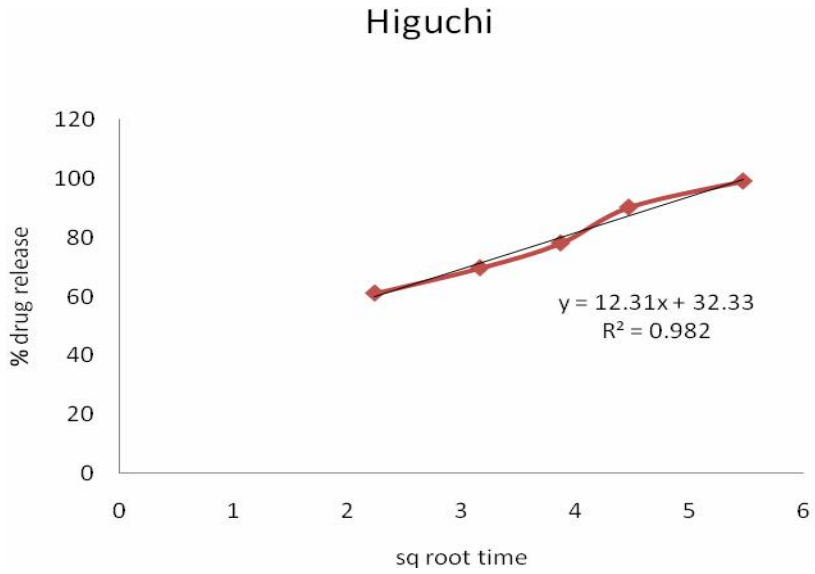


Fig. 28 Graph for the Formulation F3-Higuchi model

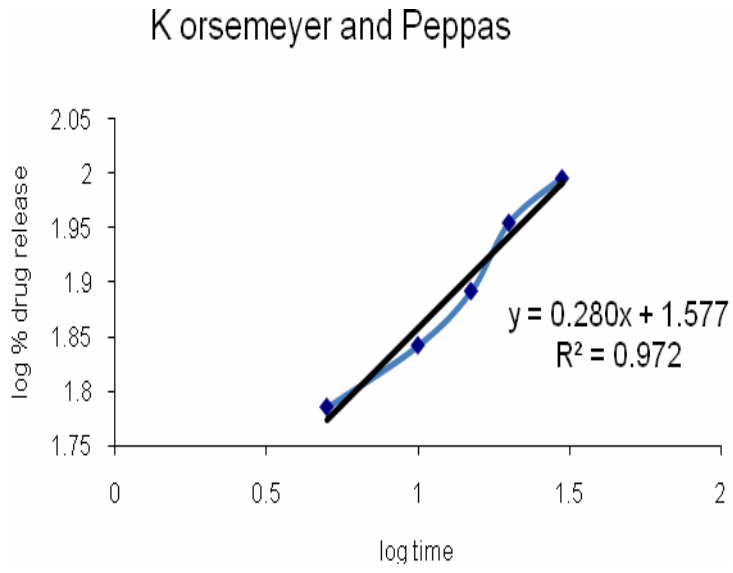


Fig. 29 Graph for the Formulation F3- Korse Meyer Peppas model

Stability Studies

Table 24 Stability Studies for F3 Formulation of Tramadol Hydrochloride ODT at 40º C /75 % RH

Batch number and stability condition	Assay (%)	Dissolution study in pH 1.2 buffer
40º C/75 % RH (Initial)	99.12%	99.18±0.16%
40º C/75 % RH (15 days)	99.64%	99.14±0.32%
40º C/75 % RH (1 month)	99.64%	99.76±0.12%

All values are expressed as mean ± SD, n=3

Table 25 Stability Studies for F3 Formulation of Tramadol Hydrochloride ODT at 40º C /75 % RH

Batch number and stability condition	Friability (%)	Hardness (kg/cm^2)	Disintegration time (sec)
40º C/75 % RH (Initial)	0.442	4.53±0.14	18
40º C/75 % RH (15 days)	0.482	4.49±0.10	18
40º C/75 % RH (1 month)	0.469	4.55±0.12	19

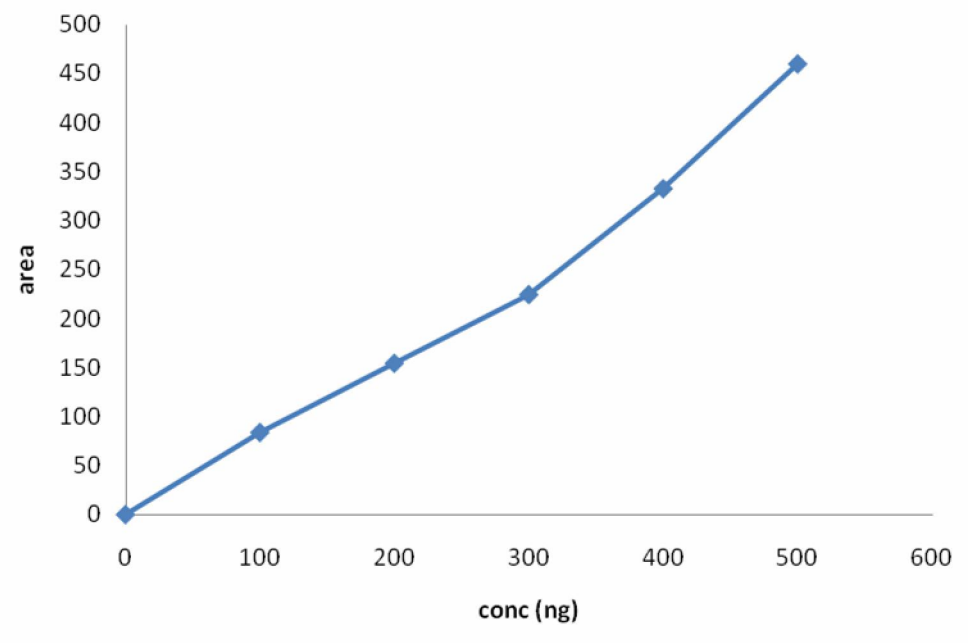


Fig. 30 *in vivo* Calibration Curve in Plasma

Table 26 *invivo* Pharmacokinetic Parameters for Marketed Formulation

Time (hr)	Area (%)	Concentration (ng/ml)
0	0	0
1	95.36	122.13
2	355.67	414.58
4	86.45	112.72
6	26.45	44.71

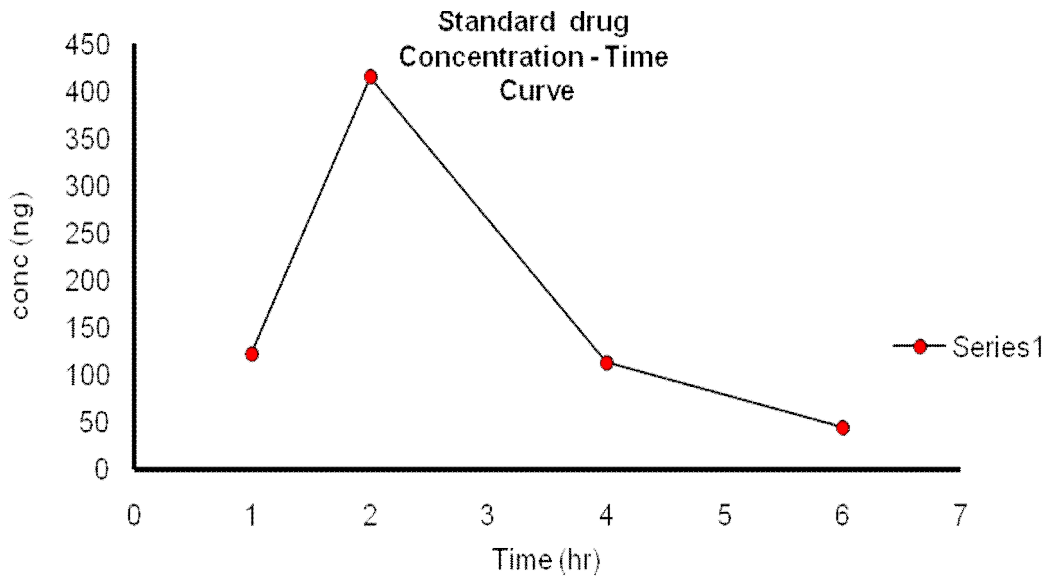


Fig. 31 *invivo* Pharmacokinetic Parameters for Marketed Formulation

Table 27 Pharmacokinetic Parameters of Marketed Product

Cmax	414.6
Tmax	2.0
$AUC_{(0\text{-}t)}$	1014.2 ng-hr/ml
$AUC_{(\alpha)}$	1110.8 ng-hr/ml
$AUMC_{(\alpha)}$	3325.1 ng-hr*hr/ml
E Phase	716.463
D/A Phase	830.576
MRT (area)	3.0 hr

Table: 28 *invivo* Pharmacokinetic Parameters for Tramadol Hydrochloride (F3)

Time (hr)	Area (%)	Concentration (ng/ml)
0	0	0
1	81.42	98.42
2	289.58	371.51
4	61.35	85.83
6	19.16	30.16

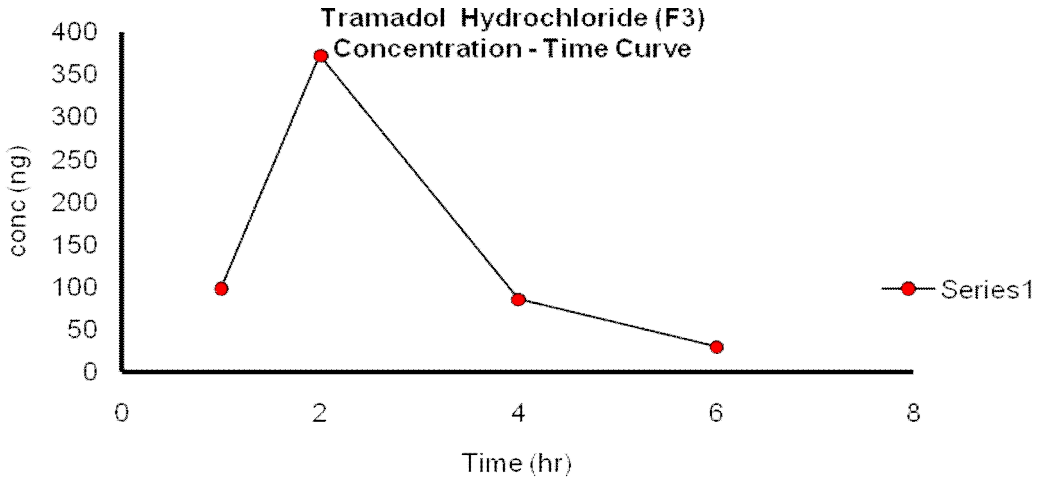


Fig: 32 *invivo* pharmacokinetic parameters for Tramadol hydrochloride (F3)

Table 29 Pharamacokinetic parameters of Tramadol hydrochloride (F3)

Cmax	371.5
Tmax	2.0
$AUC_{(0\text{-}t)}$	857.5 ng-hr/ml
$AUC_{(\alpha)}$	915.2 ng-hr/ml
$AUMC_{(\alpha)}$	2536.8 ng-hr*hr/ml
E Phase	695.112
D/A Phase	772.892
MRT (area)	2.8 hr

7. Discussion

7.1 *Raw Material Analysis of Tramadol Hydrochloride*

The experimental work started with raw material analysis of Tramadol hydrochloride. Parameters of Tramadol HCl given in the I.P were in compliance and reported in the **Table 9.**

7.2 *Compatibility Study with Excipients*

Fig 4 shows the FTIR spectra of plain Tramadol Hydrochloride

IR spectra of pure Tramadol HCL showed bands at 3000 for aliphatic C-H stretch, 2930 for CH_2 absorptions, for isopropyl group shows bands near 1170 and 1145.

IR spectra of drug and excipients physical mixture shown in **Fig 5-15** also revealed that no considerable change was observed in bands of Tramadol HCl; hence it indicates the absence of interaction between the drug and excipients used in the tablet.

7.3 *Standard Calibration Curve for Tramadol Hydrochloride*

The calibration curve of Tramadol hydrochloride in 0.1M HCl was derived from the concentration and corresponding absorbance values. Linear regression analysis gave the equation for the line of best fit as Y=0.006X+0.005. Linearity was observed in the concentration range between 20 to 100µg/ml. The values were shown in **Table 10** and **Fig 16.**

7.4 *Formulation Development*

Tramadol hydrochloride is opoid analgesic; attempts have been made to develop the oral dispersible tablets. The superdisintegrants used were Crospovidone, Croscarmellose sodium and SSG used as disintegrating agents which decreases the

disintegrating time and the effect of superdisintegrants on the drug release was studied.

7.5 *Preparation of Oral Dispersible Tablets*

Tramadol Oral Dispersible Tablets were prepared using different percentages of Crospovidone, Croscarmellose sodium and SSG as superdisintegrants by direct-compression method.

The granules prepared using Crosspovidone for compression of orally disintegrating tablets was evaluated. Angle of repose was in the range of 19.69±0.02 to 21.98±0.03. Bulk density & Tapped density has 0.289±0.023 to 0.309±0.0210 & 321±0.012 to 0.348±0.02. Compressibility index & Hausner's ratio was found to have in limit of 7.78±0.001 to 13.47±0.002 & 1.084±0.032 to 1.155±0.04. These values indicate that the prepared granules exhibited good flow properties. The results were shown in **Table 11.**

The granules prepared by using Crospovidone were compressed to tablets and tablets are tested for its physical characteristics. The thickness of the tablets was in the range of 3.14±0.012 to 3.62±0.016. The friability has 0.442 to 0.501. The hardness & weight variation is in between 3.48±0.12 to 5.65±0.11 & 299±0.14 to 305±0.25. The wetting time & Disintegration time showed the values in the range of 23 to 75 & 18 to 31. The drug content varied in between 98.23 to 99.12. The results are shown in **Table 12-13.**

The granules prepared using Crosscarmellose sodium for compression of orally disintegrating tablets was evaluated. Angle of repose was in the range of 20.79±0.05 to 22.31±0.001. Bulk density & Tapped density was found to have in the range of 0.293±0.023 to 0.312±0.032 & 0.316±0.023 to 0.375±0.012. Compressibility index & Hausner's ratio lie in between 7.27±0.012 to 13.74±0.023 & 1.078±0.012 to 1.159±0.0041. These values indicate that the prepared granules exhibited good flow properties. The results were shown in **Table 11.**

The granules prepared by using Croscarmellose sodium were compressed to tablets and tablets are tested for its physical characteristics. The thickness of the tablets was in between 3.27±0.03 to 4.14±0.14. The friability & hardness of the tablets was 0.364 to 0.486 & 3.51±0.12 to 4.53±0.14. The weight variation of the tablets lies in the range 302±0.24 to 305±0.43. The wetting time of the tablets was in the range of 29 to 35. Disintegrating time of the tablets was in the range of 20 to 29. The drug content varied in between 98.99 to 101.76. The results are shown in **Table 12-13.**

The granules prepared using Sodium starch glycolate for compression of orally disintegrating tablets were evaluated. Angle of repose was in the range of 19.76±0.03 to 22.24±0.04. Bulk density & Tapped density was in the between 0.281±0.041 to 0.318±.021 & 0.324±0.012 to 0.370±0.021. Compressibility index was in range of 8.35±0.002 to 17.02±0.001. Hausner's ratio was in the range of 1.091±0.031 to 1.205±0.012. These values indicate that the prepared granules exhibited good flow properties. The results were shown in **Table 11.**

The granules prepared by using Sodium starch glycolate were compressed to tablets and tablets are tested for its physical characteristics. The thickness of the tablets was in the range of 3.76±0.01 to 4.15±0.13. The friability of the tablets was found to be in between 0.389 to 0.423. The hardness of the tablets was in the limit of 4.23±0.16 to 4.79±0.14. The weight variation of the tablets was in the range of 298±0.18 to 306±0.41. The wetting time & Disintegrating time lies in between 27 to 31 & 26 to 32. The drug content varied in between 98.41 to 101.76. The results are shown in **Table 12-13.**

7.6 *Invitro Dissolution Studies*

On immersion in 0.1M HCl, pH 1.2 solution at 37 ± 0.5^{0} c all oral dispersible tablets remained buoyant up to 30 min.

7.6.1 Effect of Crospovidone on Drug Release

F1, F2, F3 were prepared by using Crospovidone as superdisintegrant and the drug release for these formulation was given in the **Table 14-16, Fig 17-19.** The release of drug for F1 at 5^{th} & 30^{th} minute was found to be 63.87% & 98.88%**.** The release of drug for F2 at 5^{th} minute was 67.31% and at 30^{th} minute 97.15%**.** The release of drug for F3 at 5^{th} & 30^{th} minute shows 61.05% & 99.18%

Crosspovidone due to their non-ionic nature, pyrolidone chemistry and porous particle morphology, will rapidly absorb water via capillary action. During tablet compaction, the highly compressible crospovidone particles become highly deformed. The deformed particles come in contact with water that is wicked into the tablet resulting in rapid volume expansion and hydrostatic pressure that cause tablet disintegration. Due its high crosslink density, crospovidone swells rapidly in water without gelling.

Other super disintegrants, like sodium starch glycolate and croscarmallose sodium have lower crosslink density and as a result, form gels when fully hydrated, particularly at higher use.

7.6.2 Effect of Croscarmellose Sodium on Drug Release

F4, F5, F6 were prepared by using Croscarmellose sodium as superdisintegrant and the drug release for these formulation was given in the **Table 17-19, Fig 20-22.** The release of drug for F4 at 5^{th} minute was 65.81% and at 30^{th} minute 94.87%**.** The release of drug for F5 at 5^{th} shows 59.11% and at 30^{th} minute was found to be 96.74%**.** The release of drug for F6 at 5^{th} minute & 30^{th} minute was 67.89% & 97.54%**.**

Croscarmellose sodium is an internally cross-linked sodium carboxymethylcellulose for use as a disintegrant in pharmaceutical formulations. The cross-linking reduces water solubility while still allowing the material to swell and absorb many times its weight in water. As a result, it provides superior drug

dissolution and disintegration characteristics, thus improving formulas subsequent bioavailability.

7.6.3 Effect of Sodium Starch Glycolate on Drug Release

F7, F8, F9 were prepared by using Sodium starch glycolate as superdisintegrant and the drug release for these formulation was given in the **Table 20-22, Fig 23-25.** The release of drug for F7 at 5^{th} minute was found to be 68.71% and at 30^{th} minute shows 98.42%**.** The release of drug for F8 at 5^{th} minute was found to be 72.49% and at 30^{th} minute was found to be 97.21%**.** The release of drug for F9 at 5^{th} minute & 30^{th} minute has 69.11% & 97.86%**.**

Sodium starch glycolate generally elastic in nature that they deform under pressure. But, with the compression forces involved in tabletting will deform it more to swell it higher. As a result it provides the dissolution.

7.7 *Stability Study*

Stability studies were conducted for the formulation F3. The stability study was performed at 40^0 C±2^0 C/75% RH for a specific period of time. The tablets were analysed for Disintegration time, Friability, Drug content, Hardness and *In vitro* dissolution studies. The overall results showed that the formulation is stable at the above mentioned storage conditions shown in **Table 24-25.**

7.8 *In vivo Studies*

In vivo studies were done to find out the pharmacokinetic parameters of the optimized formulation with the market product.

The Cmax for the innovator product was found to be 414.58ng/ml and for the Tramaol hydrochloride (F3) was found to be 371.51ng/ml. The concentration of the innovator product and Tramadol hydrochloride (F3) in plasma has nearly same.

The Tmax of the innovator product and Tramadol hydrochloride (F3) shows at 2^{nd} hour. $AUC_{(0-t)}$ for the innovator product and Tramadol HCl (F3) was 1014.2 ng-hr/ml & 8575.5 ng-hr/ml. $AUMC_{(\alpha)}$ shows 332.1 ng-hr^{*}hr/ml & 2536.8 ng-hr^{*}hr/ml for innovator product and Tramadol HCl.

Summary

Chapter 1(P-1) begins with a general introduction presenting an overview of oral dispersible tablets, in the part of the introduction the advantages, disadvantages of oral dispersible tablets were discussed thoroughly. Introduction shows the topic selected was worth investigating in the field of search.

Chapter 2(P-19) described the literature review carried out for selected drug, superdisintegrants and design and evaluation of oral diapersible tablets.

Chapter 3(P-29) detailed the aim and objective of the present study.

Chapter 4(P-30) detailed the information of the selected drug, and also excipients used in formulating oral dispersible tablets.

Chapter 5(44) described the plan of work.

Chapter 6(45) deals with the methodology followed for the preparation of oral dispersible tablet after raw material analysis and drug excipient compatibility studies. The detailed procedure for the preparation and evaluation of oral dispersible tablet was mentioned.

Chapter 7(62) shows the results and detailed discussion of all the formulations all the quantitative and qualitative parameters were analyzed. The raw material analysis was carried out as per I.P and which met with specifications of I.P. The Drug-Excipient compatibility study was done and found to have no interaction.

The physical charactersistics was done for all the formulations and the results were found to be satisfactory. Invitro dissolution studies were done for Tramadol HCL oral disintegrating tablet prepared with different concentrations of Crospovidone, Croscarmellose sodium and SSG were compared and discussed. Formulation F3 was found to have less disintegration time and maximum drug release with in 30 mins.

Stability studies were carried out for F3 by keeping the tablets at 40^0 C ± 2^0 C, 75% ± 5% RH for specific period of time. The physical parameters and drug release of F3 were not altered much on storage conditions for specific period of time which shows that the optimized formulation is found to be stable.

Invivo studies were done to find out the pharmacokinetic parameters of the optimized formulation with the marketed product.

Conclusion

The formulation containing 50mg of Tramadol hydrochloride was prepared as orally dispersible tablet. These techniques are particularly useful for geriatrics and pediatrics can be taken without the aid of water.

The optimized formulation have consistent release profile to provide the disintegration with in one minute by Crospovidone (F3).The short term stability study also indicates no change in the physical characteristic of drug content.

The comparision of pharmacokinetic parameters between the ODTs Tramadol HCl and conventional tablet, showed no major changes in the pharmacokinetic parameters. Hence, it can be concluded that the ODTs of Tramadol HCl was successfully developed and evaluated.

Bibliography

1. Brahmankar D M Jaiswal S B, Biopharmaceutics and Pharmaceutics, 1st Edition, 1995. P. 335.

2. Howard C Ansel, Nicholas G Popvich, Loyd V Allen, Pharmaceutical Dosage Forms and Drug Delivery System, 1st Edition, 1995. P. 78.

3. Dobetti L Fast melting tablets: Developments and technologies; Pharm Tech 2001; P. 44-50.

4. Bhandari S, Mittapalli RK, Ganu R, Rao. YM Orodispersible tablets: An overview. Asian Journal of Pharmaceutics, 2008; 2(1):2-11.

5. Debjit Bhowmik, Chiranjib.B, Krishnakanth, Pankaj, R.Margret Chandira, Journal of Chemical and Pharmaceutical Research, 2009, 1(1): 163-177.

6. Tanmoy Ghosh, Amitava Ghosh and Devi Prasad; A review on new generation Oral Dispersible Tablets and its future prospective, Int. J. Pharmacy and Pharmaceutical Sciences. 2011 Vol3, Issue 1.

7. http://www.newdruginfo.com/pharmacopeia/bp2003

8. Tanmoy Ghosh, Amitava Ghosh and Devi Prasad; A review on new generation Oral Dispersible Tablets and its future prospective, Int. J. Pharmacy and Pharmaceutical Sciences. 2011 Vol3, Issue 1.

9. Abdul Sayeed, Mohd.Hamed Mohiuddin; Mouth dissolving tablets: An Overview, International Journal of Research in Pharmaceutical and Biomedical Sciences, 2011 Vol. 2 (3).

10. Yourong Fu, Shicheng Yang, Seong Hoon Jeong, Susumu Kimura,& Kinam Park; Orally Fast Disintegrating Tablets: Developments, Technologies, Taste-Masking and Clinical Studies, Critical Reviews in Therapeutic Drug Carrier Systems, 2004, 21(6) 433–475.

11. Saxena Vaibhav, Khinchi Mahaveer Pr, Gupta MK, Agarwal Dilip and Sharma Natasha. Orally Disintegrating Tablet: Friendly Dosage Form. IJRAP 2010, 1(2) 399-407.

12. Amin A F, Shah T J, Bhadani M N, Patel M M, Emerging trends in orally disintegrating tablets, 2006.

13. Renon J P and Corveleyn S, Freeze-dried rapidly disintegrating tablets, 2000, 719.

14. Lailla J K., Sharma A H, Freeze-drying and its applications, Indian Drugs, 1993, 31, 503-513.

15. Seager H, Drug delivery products and zydis fast dissolving dosage form, J. Pharm; 1998, 50, 375-382.

16. Masaki K, Intrabuccaly disintegrating preparation and production, 1995.

17. Pebley W S, Jager N E and Thompson S J, Rapidly disintegrating tablets, 1994.

18. Allen L V and Wang B, Method of making a rapidly dissolving tablet, 1997.

19. Allen L V and Wang B, Process for making a particulate support matrix for making rapidly dissolving tablets, 1996.

20. Heinmann H and Rothe W, Preparation of porous tablets, 1975.

21. Knistch K W, Production of porous tablets, 1979.

22. Roser B J and Blair J, Rapidly soluble oral dosage form, method of making same and composition, 1998.

23. Lachmann L, Liebermann H A and Kiang J L, The theory and practice of Industrial Pharmacy, 3rd Edition, Varghese Publishing House, Bombay, 1998, 430-440.

24. Yarwood R J, Kearny K and Thomson A R, Process for preparing solid dosage form for unpalatable pharmaceuticals, 1998.

25. Parul B Patel, Amit Chaudhary and G D Gupta, Fast Dissolving Drug Delivery Systems: 2006.

26. Suresh B Borsadia, David Halloran and James L Osborne, Quick-dissolving films – A novel approach to drug delivery, 2006.

27. Mishra B, Panigrahi D and Baghel S, Mouth dissolving tablets: an overview of preparation techniques, evaluation and patented technologies, J. Pharm. Res; 2005, 4(3), 33-38.

28. Gregory G K E, Peach G M and Dumanya J D; Method for producing fast dissolving dosage form, 1983.

29. Mizumoto T, Masuda Y and Fukui M; Intrabuccaly dissolving compressed moldings and production process, 1996.

30. Robin H Bogner and Meghan F Wilkosz, Fast-Dissolving Tablets, 2006.

31. Bhaskaran S and Narmada, G V; Orally disintegrating tablets, Indian Pharmacist, 2002, 1(2), 9-12.

32. Tablets: Formulation of tablets/Disintegration, 2006.

33. Shah U and Augsburger L; Evaluation of the functional equivance of crospovidone NF from different sources: standard performance test, Pharm. Develop. Tech; 2001, 6, 419-430.

34. Swarbrick J, Boylan J, Encyclopedia of Pharmaceutical technology; 2nd Ed., Marcel Dekker, NY; 2002, 2623-2638.

35. http://formulation.vinensia.com/2011/10/superdisintegrants-used-in-tablet.html.

36. http://en.wikipedia.org/wiki/Orally_disintegrating_tablet.

37. Asija Rajesh, Shah Smit, Patel Nikunj, Laddha Jayesh, Asija Sangeeta, Katariya Sandeep, Formulation, Development & Evaluation Of Orodispersible Tablets Of Tramadol Hydrochloride; IJSPER, 2012 Vol.1 (2), 47-51.

38. Mansing G Patil, Suhas M Kakade and Sandhya G Pathade, Formulation and evaluation of orally disintegrating tablet containing tramadol hydrochloride by mass extrusion technique. Journal of Applied Pharmaceutical Science; 2011, 01 (06); 178-181.

39. Ganure Ashok L, Dangi Amish A Patel Pinkal Kumar, Manish Kumar Rai, 5Aravadiya Jigar P. Preparation and evaluation of tramadol hydrochloride fast dispersible tablet by using compression technique, IJPI's Journal of Pharmaceutics and Cosmetology; 2011 Vol 1:2.

40. Swathi S, Neeharika V, and Lakshmi PK, Formulation and evaluation of fast dissolving tablets of freely and poorly soluble drug with natural and synthetic super disintegrants. Drug Invention Today, 2011, 3(10), 250-256.

41. Mahaveer Pr Khinchi, M.K.Gupta, Anil Bhandari, Natasha Sharma, Dilip Agarwal, Design and development of Orally Disintegrating Tablets of Famotidine Prepared by Direct Compression Method Using Different Superdisintegrants. Journal of Applied Pharmaceutical Science; 2011, 01 (01); 50-58.

42. Parikh Bhavik AnjanKumar, M Najmuddin, Kulkarni Upendra and Hariprasanna RC Formulation and Evaluation of Lornoxicam Fast Dissolving Tablet; IJRP; 2011, 2(4) 130-133.

43. Manreet Chawla and Ganga Srinivasan, Evaluation of galen IQ polymer in Tramadol Hydrochloride orally disintegrating tablet. International Journal of Drug Delivery; 2011, (3) 439-455.

44. Dr. C S R Lakshmi, Nitesh J Patel, Hitesh P Patel, Sagar Akul, Formulation And Evaluation Of Oral Dispersible Tablets Of Cinnarizine Using Sublimation Technique. International Journal of Pharmaceutical Sciences Review and Research, 2011, Volume 6, Issue 2.

45. Sagar Shanti, Patel Jitendra, Nanjwade B, Ali Mehraj, Kumar D Bharat and Mohanty Sivasankar, Formulation and Evaluation of Subcutaneous Implantable Drug Delivery System of Tramadol. International Journal of Research in Pharmaceutical and Biomedical Sciences, 2011, Vol. 2 (1).

46. Yash Paul, Sarvan Tyagi and Bhupinder Singh, Formulation and Evaluation of Oral Dispersible Tablets of Zidovudine with different Superdisintegrants**.** International Journal of Current Pharmaceutical Review and Research; 2011 Volune 2, Issue 2.

47. Prakash Goudanavar, Shivam H Shah, Doddayya Hiremath, Development and Characterization of Lamotrigine Orodispersible Tablets: Inclusion Complex with Hydroxypropyl B Cyclodextrin. International Journal of Pharmacy and Pharmaceutical Sciences; 2011, Vol 3, Issue 3.

48. Dayakar Rao Kalakuntla, Mahesh Gada, Gaytri kulkarni, Design and development of taste masking lornoxicam orodispersible tablet; IJPI's Journal of Pharmaceutics and Cosmetology; 2011 Vol 1: 2.

49. Sunitha S, Amareshwar P, Santhosh Kumar M, Chakravarti P, Preparation and Evaluation of Tramadol Hydrochloride Microspheres by Coacervation Phase Separation Technique Using Various Solvents And Non-Solvents. Journal of Global Pharma Technology; 2011, 3(4):33- 41.

50. Joshi N C, Ahmad Z, Mishra S.K and Singh R, Formulation and Evaluation of Matrix Tablet of Tramadol Hydrochloride; Ind J Pharm Edu Res, 2011, Vol 45, Issue 4, 360.

51. Shankar Avulapati, Prof. Anup Kumar Roy, K R Shashidhar,ThoutReddy UgendarReddy, Formulation And Evaluation Of Taste Masked And Fast Disintegrating Losartan Potassium Tablets. Int. J. Drug Dev. & Res; 2011, 3 (1):45-51.

52. D. Nagendra Kumar, Raju S. A, Shirsand S. B, Para M. S, Formulation design of novel Fast Dissolving Tablets of Granisetron Hydrochloride using Disintegrants Blends for improved efficacy; IJRAP 2010, 1(2) 468-474.

53. Suhas M. Kakade, Vinod S. Mannur, Ravindra V. Kardi, Ketan B. Ramani, Ayaz A. Dhada, Formulation And Evaluation Of Orally Disintegrating Tablets of Sertraline; IJPRD, 2010, Vol-1, Issue-12.

54. Sunil H. Makwana, Dr. L.D.Patel, Tejas B. Patel, Timir B Patel, Tushar R. Patel, Formulation and Evaluation of Taste Masked Orodispersible Tablets of Ondansetron Hydrochloride. J. Pharm. Sci. & Res; 2010, Vol.2 (4), 232-239.

55. Suhas M. Kakade, Vinodh S. Mannur, Ketan B. Ramani, Ayaz A. Dhada, Chirag V. Naval, Avinash Bhagwat, Formulation and evaluation of mouth dissolving tablets of losartan potassium by direct compression techniques; Int. J. Res. Pharm. Sci; 2010, Vol-1, Issue-3, 290-295.

56. P. P. Sawarikar, B. K. Sridhar and S. Shivkumar, Formulation and Evaluation of Fast Dissolving or Disintegrating Tablets of Isoxsuprine Hydrochloride. Journal of Current Pharmaceutical Research 2010; 3(1): 41-46.

57. Vineet Bhardwaj, Mayank Bansal and P.K. Sharma, Formulation and Evaluation of Fast Dissolving Tablets of Amlodipine Besylate Using Different Super Disintegrants and Camphor as Sublimating Agent; American-Eurasian Journal of Scientific Research; 2010, 5 (4): 264-269.

58. S. K. Sheth, S. J. Patel And J. B. Shukla, Formulation And Evaluation Of Taste Masked Oral Disintegrating Tablet Of Lornoxicam; International Journal of Pharma and Bio Sciences; 2010, V1 (2).

59. Margret Chandira .R. Jaykar .B.,Chakrabarty B. L, Formulation and evaluation of Orodispersible tablets of terbutaline sulphate. Drug Invention Today; 2010, 2(1), 31-33.

60. N.Kanakadurga devi, A.Prameela Rani, B.Sai Mrudula, Formulation and evaluation of oral disintegrating tablets of montelukast sodium: effect of functionalityof superdisintegrants. Journal of Pharmacy Research; 2010, 3(4), 803-808.

61. Metker Vishal, Kumar Anuj, Pathak Naveen, Padhee Kumud, Sahoo Sangram, Formulation and Evaluation of Orodispersible Tablets of Lornoxicam. Int. J. Drug Dev. & Res; 2011, 3 (1): 281-285.

62. Vinayak S. Modi,Yogesh S. Thorat, Shashikant C. Dhavale, Formulation And Evaluation Of Controlled Release Delivery Of Tramadol Hydrochloride Using 32- Full Factorial Design. International Journal of ChemTech Research; 2010, Vol.2. P. 669-675.

63. Raval S.B., Prajapati R., Shah N.V., Ghelani T.K., Seth A.K., Saini V., Deshmukh G.J., Randive S. Formulation And Evaluation Of Tramadol Hydrochloride Mouth Dissolving Tablet, Journal of Global Pharma Technology; 2010, 2(11): 17-22.

64. C.P. Jain and P.S. Naruka, Formulation and Evaluation of Fast Dissolving Tablets of Valsartan**.** International Journal of Pharmacy and Pharmaceutical Sciences; 2009, Vol. 1, Issue 1.

65. Anupama Kalia, Shelly Khurana, Neena Bedi, Formulation and Evaluation of Mouth Dissolving Tablets Of Oxcarbazepine. International Journal of Pharmacy and Pharmaceutical Sciences; 2009, Vol. 1.

66. Parmar R.B, Baria A.H, Tank H.M, Faldu S.D, Formulation and Evaluation of Domperidone Fast Dissolving Tablets. International Journal of PharmTech Research; 2009, Vol.1. P. 483-487.

67. Amrit B. Karmarkar, Indrajeet D. Gonjari, Avinash H. Hosmani, Pandurang N. Dhabale, Ravindra D. Thite, Preparation and *in vitro* evaluation of lyophilized nasal inserts of tramadol hydrochloride. Asian Journal of Pharmaceutical Sciences; 2008, 3 (6): 276-283.

68. Adamo Fini, Valentina Bergamante, Gian Carlo Ceschel, Celestino Ronchi, Carlos Alberto Fonseca de Moraes, Fast dispersible/slow releasing ibuprofen tablets. European Journal of Pharmaceutics and Biopharmaceutics; 2008 (69) 335–341.

69. B. Mishra, Bharti V. Bakde, P. N. Singh and P. Kumar, Development and In-vitro Evaluation of Oral Sustained Release Formulation of Tramadol Hydrochloride**.** Acta Pharmaceutica Sciencia; 2006 (48) 153-166.

70. www.drugbank.com Accessed; 2007.

71. www.wikipedia.org Accessed; 2007.

72. Tiwari S, Murthy T, Pai M. Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix systems. AAPS PharmSciTech; 2003; 4(3): E31.

73. Handbook of Pharmaceutical excipients 6th edn; 2009, 210-214.

74. Handbook of Pharmaceutical excipients 6th edn; 2009, 208-210.

75. Handbook of Pharmaceutical excipients 6th edn; 2009, 206-217.

76. Handbook of Pharmaceutical excipients 6th edn; 2009, 663-665.

77. Handbook of Pharmaceutical excipients 6th edn; 2009, 129-132.

78. Handbook of Pharmaceutical excipients 6th edn; 2009, 185-188.

79. Handbook of Pharmaceutical excipients 6th edn; 2009, 48-49.

80. USP-34 NF-29, 2011; volume-1, 964.

81. USP-34 NF-29, 2011; volume-1, 965.

82. S. T. Birhade, V. H. Bankar, P. D. Gaikwad, S. P. Pawar, Preparation and Evaluation of Cyclodextrin Based Binary Systems for Taste Masking. International Journal of Pharmaceutical Sciences and Drug Research; 2010; 2(3): 199-203.

83. S. K. Sheth, S. J. Patel1 and J. B. Shukla, Formulation and Evaluation of Taste Masked Oral Disintegrating Tablet of Lornoxicam. International Journal of Pharma and Bio Sciences; 2010 V 1(2).

84. Subrahmanyam CVS, Thimmasetty J, Shivanand KM, Vijayendraswamy SM. Laboratory manual of industrial pharmacy. Delhi: Vallabh Prakashan; 2006.

85. Lachmann L, Liebermann HA, Kiang JL. The theory and practice of industrial pharmacy. 3rd ed. Bombay: Varghese Publishing House; 1998:430-40.

86. Lieberman HA, Lachman L, Schwartz JB. Pharmaceutical Dosage Forms: tablets. 2nd ed:New York: Marcel Dekker, Inc.; 2005 (3) 77-160.

87. Subramanyam CVS, Thimmasetty J. Laboratory manual of physical pharmaceutics. Delhi; Vallabh Prakashan: Delhi; 2005.

88. Indian Pharmacopoeia. Government of India, Ministry of health and family welfare, Published by the controller of publications, Delhi, 2007; Volume I &II.

89. Schwarw B.J., Simonelli A.P., Miguchi W.I., Drug release from wax matrices analysis of data with first order kinetics and with the diffusion controlled model, Journal of Pharmaceutical Sciences, 1998, 57, 274 – 277.

90. Varelas C.G., Dixon D.G., Steiner C., Zero order release from biphasic hydrogels, Journal of Control Release, 1995, 34, 185 – 192.

91. Colombo P., Bettini Release., Catellani P.L., Drug volume fraction profile in the gel phase and drug release kinetics in hydroxypropyl methyl cellulose matrices containing a soluable drug, European Journal of Pharmaceutical Sciences, 2002, 86, 323 – 328.

92. D R Gross, W G Kramer, F McCord, C Wagner-Mann, Pharmacokinetics of orally administered tramadol in domestic rabbits. American Journal of Veterinary Research; 1986, Volume: 69, Issue: 9. P. 2053-2056.

93. Muhammad Naeem Aamira, Mahmood Ahmada, Naveed Akhtara, Ghulam Murtazaa, Shujaat Ali Khana, Shahiq-uz-Zamana, Ali Nokhodchi, Development and in vitro–in vivo relationship of controlled-release microparticles loaded with tramadol hydrochloride. International Journal of Pharmaceutics; 2011(407) 38–43.